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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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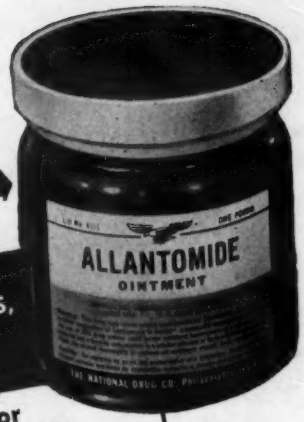

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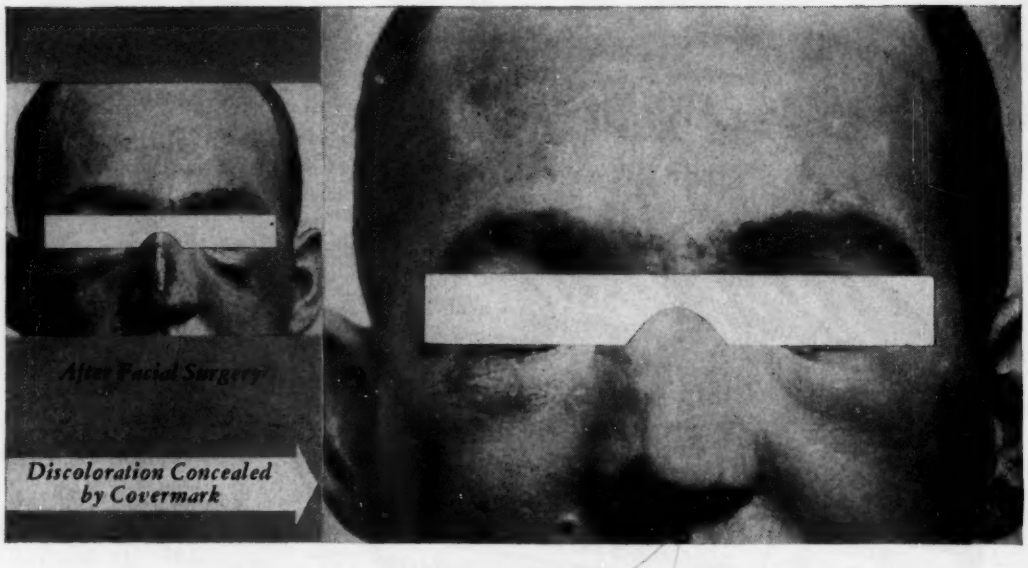

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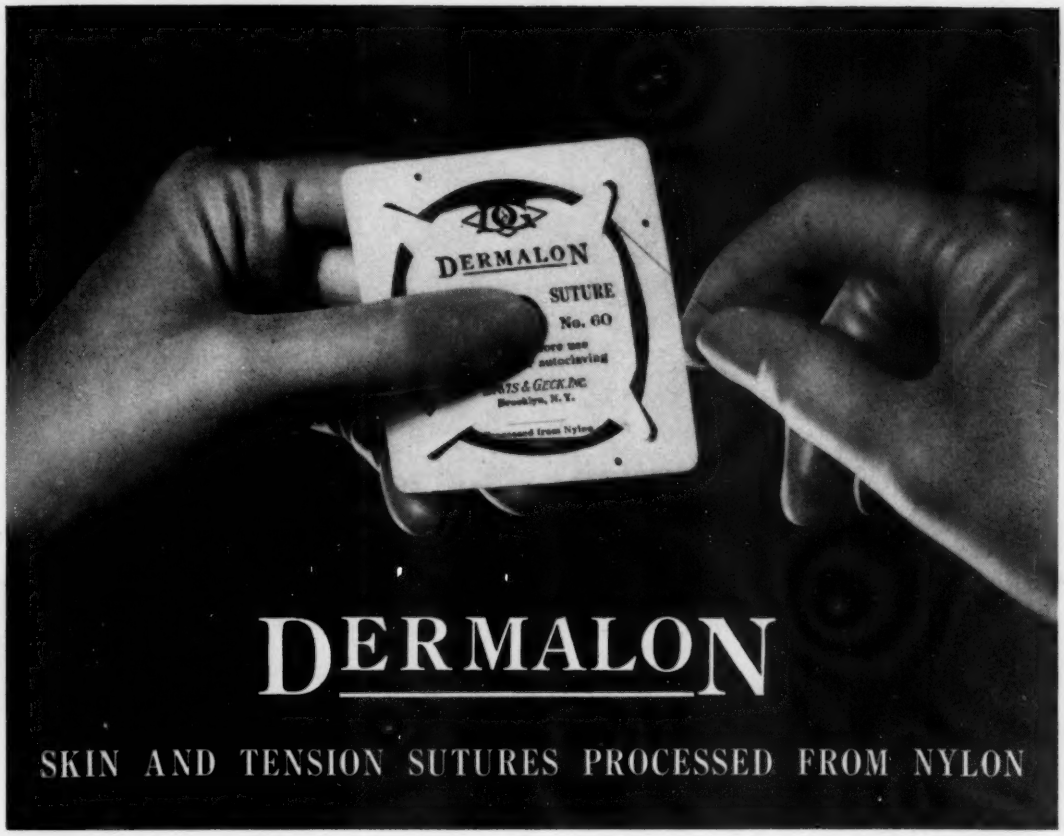

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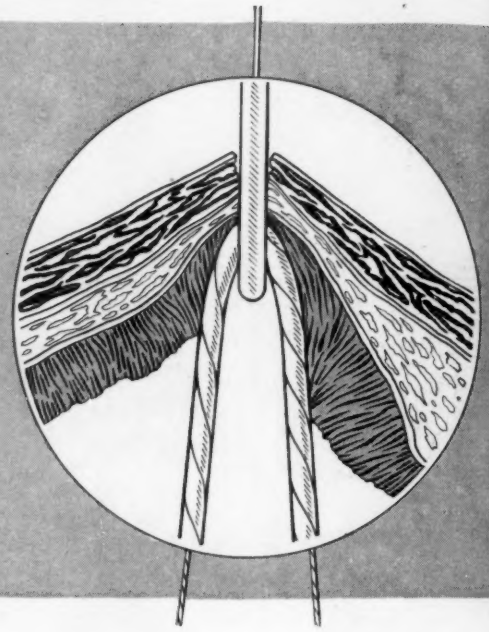

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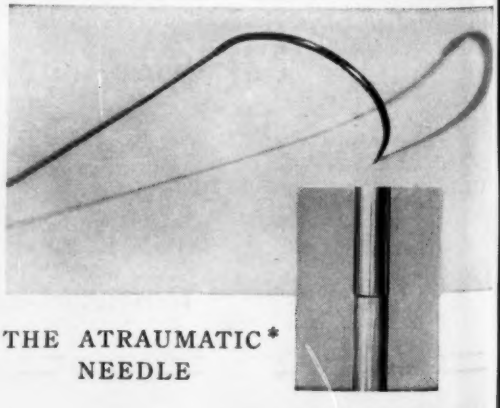

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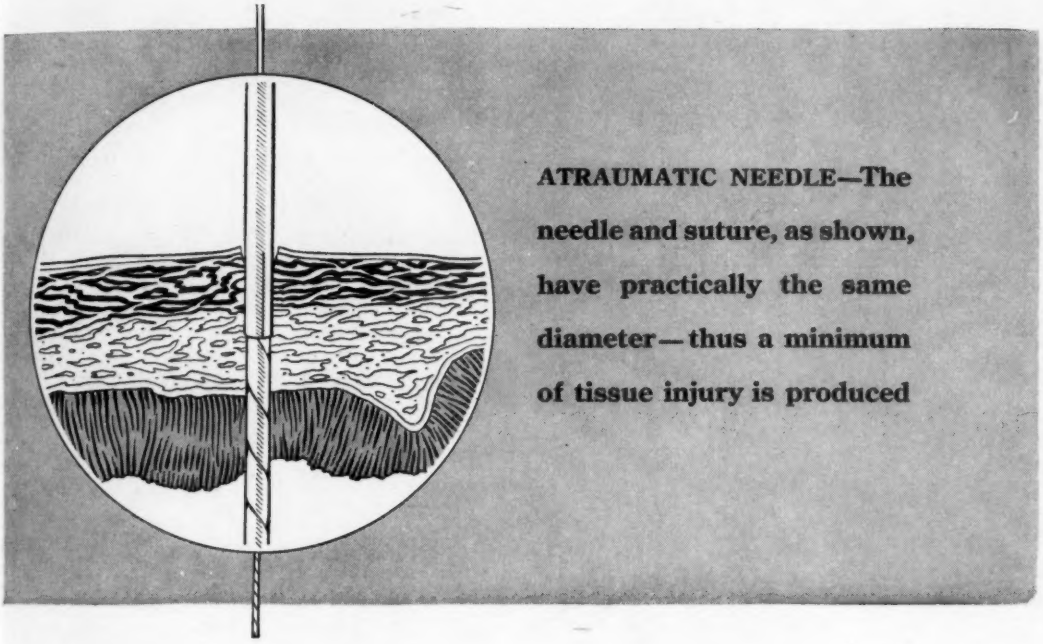

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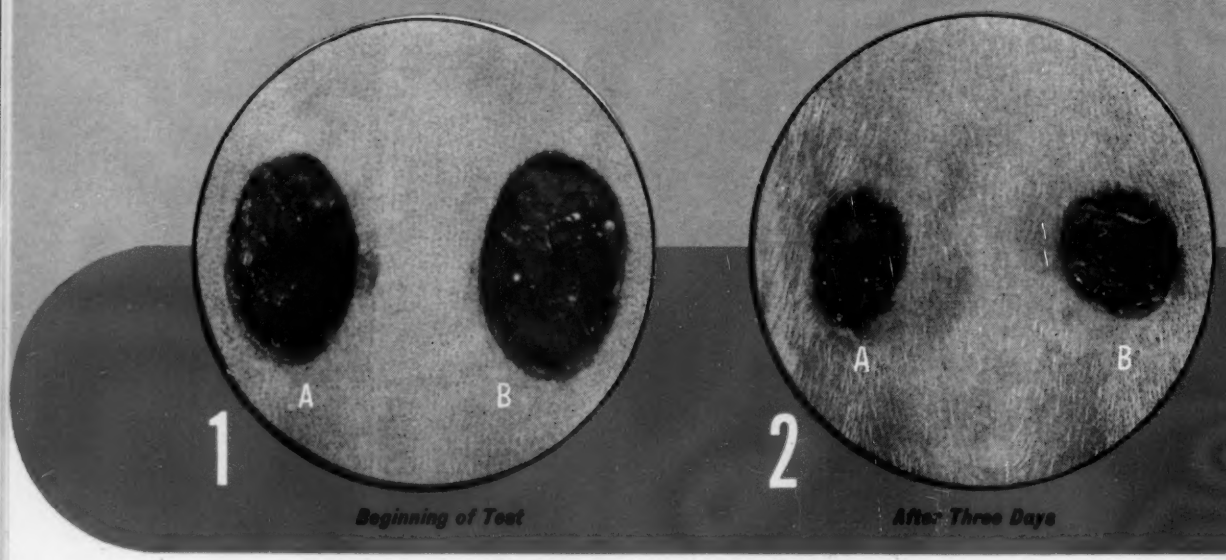

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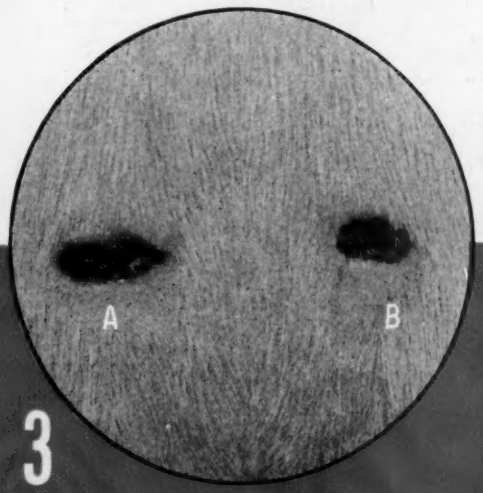

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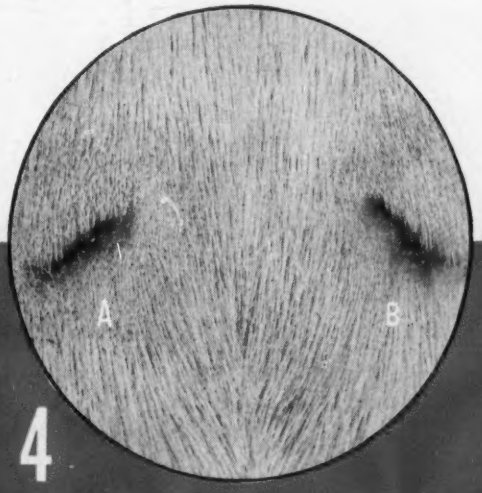

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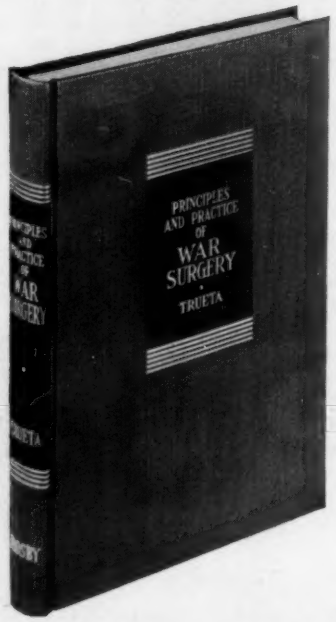

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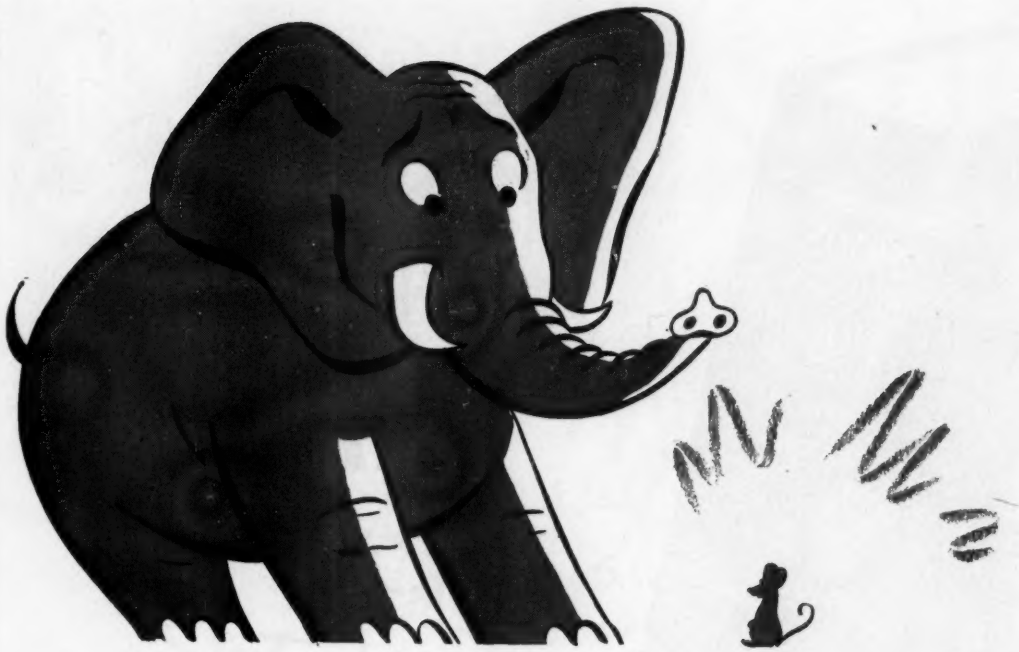

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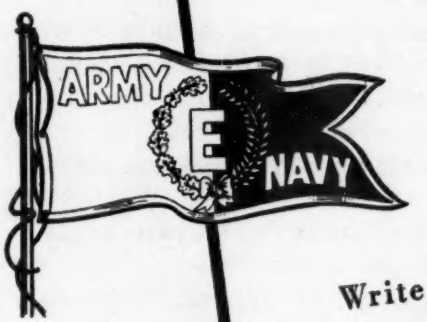

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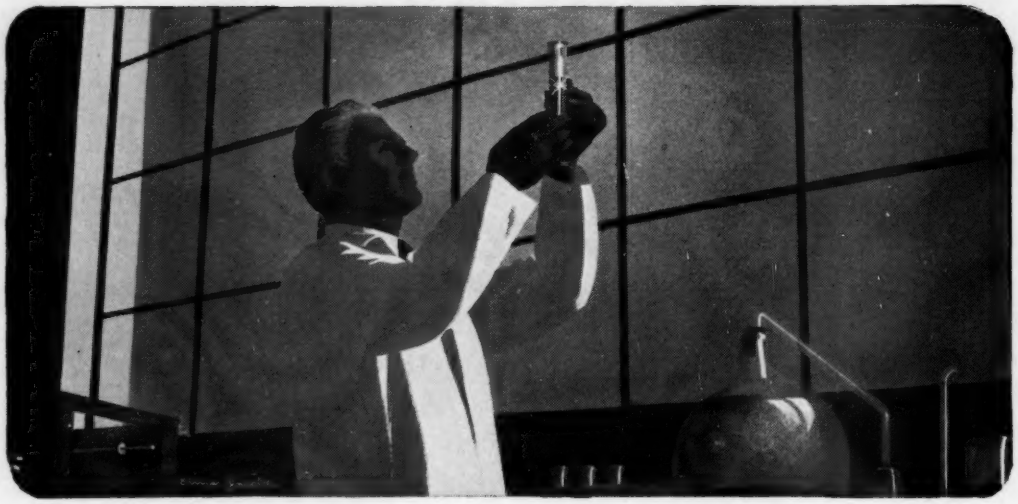

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(From the Department of Neurological Surgery, Jewish Hospital of Brooklyn)

EFFORTS to ameliorate epilepsy by augmenting the circulation of the cerebral cortex are not new. Among the earliest attempts were those of Alexander,[1] who tried to accomplish this result by cervical sympathectomy. Penfield[7] has called attention to a case in which "removal of the superior sympathetic ganglia, decortication of the carotid artery, removal of the ganglia upon the vertebral artery, and decortication of that artery" on one side converted a case of generalized epilepsy into unilateral epilepsy which continued for a year. This same investigator,[8] on the basis of his experiences at the operating table, concluded that "the one constant visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation. The vasomotor spasms and changes seen so characteristically in the cerebral cortex of epileptics are due to vasomotor reflexes but reflexes which are probably not subserved by autonomic neurones placed outside of the cranial cavity." It would thus appear that the failure of cervical sympathectomy to effect a sustained improvement may be attributable to the fact that the resultant enhancement of the cortical circulation is not substantial or lasting. That this possibility is the case is also suggested by experiments disclosing that only slight cerebral vasoconstriction can be produced by cervical sympathetic stimulation.[5]

That a sustained revascularization of the brain is possible in lower animals has been proved by German and Taffel,[6] who accomplished this result by grafting a scarified muscle flap onto a brain surface denuded of its arachnoid investment, an application of the principle previously applied to the vascularization of organs other than the brain, notably the heart[2] and kidney.[4] Using monkeys as experimental animals they were able to demonstrate new patent anastomotic channels as early as three

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weeks following operation. These investigators suggested the possibility of this procedure for such conditions obtaining in humans as "cerebral arteriosclerosis, recurrent cerebral thromboses, and intracranial aneurysms requiring internal carotid ligation."

The ability to enhance the circulation of the brain in lower animal forms naturally raises the question of the utilization of encephalomyopexy in the human subject. In view of the evidence of irreversibility of destruction of Betz cells, it appeared too sanguine to hope that hemiplegias based on more than mere physiologic interruption could be favorably influenced by such a procedure. But the possibilities for epilepsy would not be governed by such limitations if the hypothesis relative to an underlying capricious cerebral vascular mechanism were substantially correct. Under such circumstances efforts to improve the cortical vasculature would appear rational.

TECHNICAL CONSIDERATIONS

To effect actual vascular anastomosis between the cortex and overlying muscle in the absence of intracranial hypertension, intervening arachnoid must be eliminated. Rather than strip it from the brain and thereby invite unfavorable hemorrhage, it was deemed preferable to accomplish the same result by lightly cauterizing the superficial portions of some of the more prominent exposed convolutions. At such points, firm anastomosis with a superimposed muscle flap could then be expected to take place.

The technical problem of swinging a pedicle flap of temporal muscle onto the cortex, without leaving a sizable bony defect, is a relatively simple one. The scalp and muscle flaps are each reflected separately. The underlying bone area is then removed en bloc. When ready for closure one wires the bone flap in place after having made a small opening at its base. The size of this defect is just sufficient to allow for the entry of muscle without constricting its pedicle.

Although the temporal muscle is deprived of its usual attachment to the skull by this operation, masticatory function is not interfered with, nor is the act of mastication accompanied by any untoward effects upon the patient. The contour of the temporal region on the operated side is not visibly altered, since the bone defect is quite small and situated in the infratemporal zone.

SELECTION OF MATERIAL

Only patients whose convulsive manifestations were quite consistently focal, or related to a local lesion such as an injury or former infection, were selected for operation. Furthermore, these phenomena had to correlate with an abnormal intracranial focus, demonstrable by pneumencephalography and/or electro-encephalography. Operation was not performed, despite these criteria, if the seizures were adequately controlled with medication.

It seemed advisable that the projected procedure be restricted

initially to a type of case in which severe convulsive manifestations were associated with a focal atrophic lesion. A case ultimately did present itself bearing criteria which were considered sufficient justification for operation, namely, a posttraumatic hemispheric atrophy with contralateral hemiparesis and jacksonian epilepsy involving the weakened limbs.

CASE 1 (Patient M. R.; J. H. B. No. 233773).—An 11-year-old girl was admitted to the hospital on Oct. 3, 1941, because of right-sided convulsions and paresis of the right limbs. She had fallen down a flight of stairs in June, 1937, following which a quadriparesis resulted. The weakness of the left limbs cleared up slowly, but there was a residual right hemiparesis.

Right-sided convulsions appeared two years following injury. They were frequently associated with unconsciousness, tongue biting, and loss of posture control. Before the institution of medication with phenobarbital, paroxysms occurred three or four times daily. On medicinal therapy their frequency was cut down to "once or twice a day several times a week." A pneumencephalogram performed during hospitalization in June, 1940, established the diagnosis of left cerebral atrophy. The patient was readmitted in October, 1941, with a history of some progression in her right-sided weakness and a persistence of convulsions. The patient had been closely observed during 1941, but despite anticonvulsant medication, the widest intervals ever noted between attacks did not exceed three days.

The positive findings on neurologic examination included moderate facetiousness and mental retardation; slight awkwardness in speech without frank dysphasia; right spastic hemiparesis (about 40 to 50 per cent impairment), somewhat more marked in the upper limb; slight atrophy of the right limbs, hyperactive tendon reflexes on the right, absent abdominal reflexes, and Babinski toe sign bilaterally.

Preoperative electro-encephalographic studies disclosed "irregularities of pattern from all areas with concentration of disturbances (constant and spasmodic) anteriorly and to the left." (Rheinberger).

Operation.—A left lateral craniotomy and encephalomyopexy were carried out on Oct. 13, 1941, under general anesthesia. The exposed brain was found to be slightly atrophic and on palpation in the sylvian region to be fairly hard, suggesting the presence of a cicatrix.

Postoperatively, the patient fared well during the first twelve hours, after which she developed a series of right-sided convulsions, which cleared up within forty-eight hours. Thereafter, the patient was subject to relatively light convulsions, separated by steadily widening interparoxysmal intervals in place of the former more intense paroxysms occurring almost daily. Recently, seizures have been limited essentially to the right hand, although the right lower limb and the right side of the face are also involved occasionally. Paroxysms now occur at intervals of two to three weeks in place of the former maximal free interval of three days. The patient and family express satisfaction with the result, both as to epilepsy and motor weakness. While this has been apparent in the former, objective study could reveal no striking improvement in the latter.

Although the patient was appreciably improved following operation, the result secured was not as good as that seen in some of the other cases. In contrast to those in which convulsions did not recur, it is noteworthy that apart from the suggestion of atrophy the brain did not present a grossly abnormal appearance at operation. This fact and the electro-encephalographic evidence of diffuse bilateral dysrhythmia, pre- and postoperatively, suggest that this type of case is less suitable for encephalomyopexy.

CASE 2 (Patient H. B.; J. H. B. No. 242057).—A 54-year-old man was admitted to the hospital on March 13, 1942, with a history of left-sided convulsions, involving the face and limbs, occurring every two to four weeks despite medication with dilantin and phenobarbital. Most of the seizures were associated with unconsciousness. In 1932, the patient had been operated upon for a subdural hematoma situated over the right cerebral hemisphere. Convulsions made their appearance about three months following operation. Pneumencephalographic studies carried out in 1934 and again in 1938 suggested the possibility of meningeal adhesions and right hemispheric atrophy. A trephine opening subsequently made over the right temporal region revealed no evidence of a recurrent subdural hematoma, but disclosed meningocerebral adhesions.

The neurologic examination revealed a paucity of positive findings. These included moderate psychomotor retardation and generalized hyperactivity of the tendon reflexes, greater on the left than on the right.

Operation.—A secondary right lateral craniotomy and encephalomyopexy were carried out on March 19, 1942. The brain at operation was the site of multiple, pitted, scarred, and atrophic areas. Most were discolored yellow and in some regions were in the nature of leptomeningeal cysts, which were evacuated where possible. Meningocerebral adhesions were present in a few places; they were not excised.

Postoperatively, the patient had an essentially uneventful convalescence. Seizures have not recurred.

This patient had a gross focal lesion underlying his jacksonian seizures. The lesion itself was not treated directly, it being much too extensive to justify excision without hazarding paralysis. The freeing of meningocerebral adhesions did not seem sufficient to explain the subsequent relief, as they accounted for only a small part of the local pathology.

CASE 3 (Patient S. M.; J. H. B. No. 245916).—A man aged 29 years entered the hospital March 31, 1942, because of convulsive seizures of not quite three years' duration. Paroxysms were of a major, generalized character associated with urinary incontinence and tongue biting. There were no focal features to the attacks. Such seizures occurred as frequently as three to four times daily when medication was not being taken. With medication paroxysms averaged about two to three a week. They were interspersed with episodes of momentary unconsciousness occurring frequently in the course of the day.

Of interest in the past history was the development of a right-sided deafness and facial weakness following a mastoidectomy in childhood.

The neurologic examination apart from the old right-sided deafness and facial weakness, disclosed a generalized hyporeflexia, with reflex activity somewhat greater in the right limbs than in the left. Laboratory studies were without significance. Pneumencephalography revealed a slight enlargement of the right lateral ventricle suggesting atrophy in the surrounding brain substance.

Operation.—A right lateral craniotomy with encephalomyopexy was carried out on April 10, 1942, under general anesthesia. The brain at operation did not appear unusual.

The patient was discharged two weeks following operation. Thereafter, seizures of a major, generalized character, without focal features, reappeared. They were less frequent and intense, and of shorter duration than formerly. In contrast to the former frequency of two to three times weekly, seizures did not occur more frequently than once a week.

This case could not be considered one of material improvement. In retrospect, it probably represented a poor selection, inasmuch as the

only indication of a focal lesion was the slight pneumencephalographic evidence of cerebral atrophy on the side where mastoiditis had formerly been present. Unlike those cases in which convulsions did not recur, the brain did not present a grossly abnormal appearance at operation.

CASE 4 (Patient S. T.; J. H. B. No. 253273).—A 31-year-old man was admitted to the hospital on April 21, 1942, with a history of right-sided convulsions, associated with unconsciousness and tongue biting, during the previous year. Seizures were not materially influenced by medication. For a year prior to the development of these paroxysms the patient had been subject to vertiginous episodes manifested by a flushing sensation in the head, accompanied by a feeling of anxiety. He had been hospitalized in 1916, following a fall from a fire escape, which rendered him unconscious. X-ray study on that occasion revealed a fissure fracture of the left parietal and temporal bones.

The neurologic examination revealed no abnormal findings. The systemic examination was likewise negative except for the elicitation of a blood pressure of 160/100. Laboratory studies were not of particular significance, except for the presence of 1 plus albuminuria. X-rays of the skull disclosed an area of about 3.5 by 4.5 cm. in the left posterior temporal region, where the irregular calcium distribution suggested a local lesion not unlike chronic osteomyelitis. Pneumencephalographic studies disclosed a normal looking ventriculosubarachnoid system. Electro-encephalography revealed "essentially normal activity except for intermittent disturbances arising from the left temporoparietal area." (Rheinberger).

Operation.—A left lateral craniotomy was performed on April 27, 1942, under avertin and local anesthesia. The brain appeared degenerated. Some meningocerebral adhesions and leptomeningeal cysts were present. After preliminary excision of the old fracture area and separation of the underlying adhesions, an encephalomyopexy was carried out.

The patient's postoperative convalescence was uneventful. Seizures have thus far not recurred.

The features in this case underlying the favorable result secured were similar to those of the other favorable cases, namely, strictly focal manifestations based on a grossly abnormal brain lesion.

CASE 5 (Patient A. B.; J. H. B. No. 249181).—A 15-year-old boy was admitted to the hospital with a history of right-sided convulsive seizures of four years' duration. Efforts to control the paroxysms with anticonvulsant medication, including phenobarbital and dilantin, were unavailing, seizures continuing to occur at about weekly intervals, interspersed with more frequent episodes resembling petit mal.

Significant in the past history was a skull fracture at the age of 6. The patient at birth had been a breech presentation and was delivered following a difficult labor lasting three days. It was believed that he sustained an intracranial hemorrhage. The patient was subject to neonatal convulsions which cleared up after two years and did not recur until more recently. Weakness of the right limbs was first noted at about 6 months of age.

Positive features on neurologic examination included an obvious psychomotor retardation (psychometric study revealed an I.Q. of 63), a palpable bony deformity of the left temporal region, right central facial weakness, slight weakness and atrophy of the right limbs, right deep hyperreflexia, and hemihypesthesia.

Significant in the work-up were the pneumencephalographic studies which disclosed a left lateral porencephaly in association with the old skull fracture and secondary skull changes.

Operation.—A left lateral craniotomy and encephalomyopexy were carried out on May 27, 1942, under general anesthesia. Multiple loculated leptomeningeal cysts

were found in the temporal region, associated with overlying thinning, scalloping, and lateral protusions of the temporal bone. The subarachnoid space was distended. The brain itself in this region was atrophic and discolored yellow. Some meningocerebral adhesions were present. A few of these were freed but no attempt at cicatricectomy was made. Some of the leptomeningeal cysts were evacuated. The area of deformity in the squamous temporal area, measuring about 3 by 2 by 2 cm., was removed.

The postoperative course was uneventful. The patient was discharged on the sixteenth postoperative day. Seizures have thus far not recurred. The slight weakness of the right limbs appears to be unchanged, although the patient believes them to be stronger than formerly.

As in the other cases where the results were favorable, there existed in this case the common denominator of strictly focal manifestations based on a grossly abnormal cerebral lesion.

COMMENT

Of the five cases operated upon, three have not been subject to recurrence of seizures during the period of followup thus far, five to seven months following operation. In the remaining two cases the frequency and intensity of the paroxysms have diminished appreciably, but it is uncertain whether this particular improvement is to be attributed to operation. The postoperative medication in all instances was maintained as close as possible to that which failed to control seizures preoperatively.

The operation was well tolerated in every instance. No resulting impairment of function was observed. Two patients who were hemiparetic prior to operation believed themselves to be stronger in the impaired limbs postoperatively. This was not borne out by objective study.

Of interest is the type of case which responded most favorably. Those in which seizures did not recur shared the common denominator of focal manifestations corresponding to a macroscopic post-traumatic cerebral lesion, such as cystic degeneration. In each instance the site of the lesion and its extent were such as not to justify surgical removal without the expectation of possible resultant impairment of function and appreciable reformation of scar tissue. The two cases in which convulsions recurred did not present comparable lesions at operation. In one the brain appeared normal. The pattern of the seizures, furthermore, was not focal. In the other, the external appearance suggested slight atrophy, and palpation indicated a possible intrinsic scar. Although the seizures in this case were of a focal pattern, repeated electroencephalographic studies indicated a diffuse dysrhythmia over both hemispheres.

The question naturally arises as to whether myopexy does not substitute one epileptogenic scar for another. It appears probable that the muscle graft, while it does encourage scar formation, carries with it sufficient circulation to differentiate it pathophysiologically from known atrophic epileptogenic lesions, which are not quite so vascular.

In this connection it is noteworthy that in the experimental animals of German and Taffel[6] "the grafts were solidly attached to the underlying brain by a vascular layer of fibroblasts which gradually assumed the characteristics of adult connective tissue cells." Nevertheless, it is perhaps significant that although the animals were observed for periods up to twenty months, convulsions were noted in only one case. They occurred in the contralateral face, neck, and arm four days following the application of a temporal muscle graft, a time at which neither collateral circulation nor appreciable scar formation were yet present. Autopsy of this animal revealed no apparent cause for the convulsions on gross examination. The paroxysms were attributed to excessive operative trauma rather than to the formation of a fibroglial scar.

It is thought that the beneficial effects thus far noted are attributable to enhancement of the cortical vasculature for reasons already alluded to. In the absence of actual visible musculoencephalic anastomosis such proof would have to await histologic or possibly angiographic studies. For the time being the possibility of its presence is based on the experimental data of German and Taffel[6] and knowledge of the accidental production of such anastomoses occasionally resulting from compound skull fractures. That the mere presence of the contiguous muscle flap has not introduced a fortuitous physicochemical factor is deducible from the studies of Block,[3] who reported on the transplantation of a wide variety of foreign bodies into the defect left by cicatricectomy. Paraffin, celluloid, muscle, fat, and fascia were all used to no avail. Not only did these fail to influence seizures, but they also failed to inhibit the reformation of scar tissue.

SUMMARY AND CONCLUSIONS

1. Reported herein is the treatment of five cases of focal epilepsy by encephalomyopexy.

2. The theoretic considerations upon which this procedure is based are discussed.

3. Of the five cases operated upon, three have not been subject to recurrence of seizures thus far. In the remaining two cases the frequency and intensity of the paroxysms have diminished only moderately. Those in which seizures did not recur shared the common denominator of focal manifestations corresponding to a gross posttraumatic cerebral lesion, of a cystic degenerative nature.

4. Two patients who had preoperative hemipareses corresponding to their cerebral lesions believed themselves to be stronger in the impaired limbs postoperatively. This was not borne out by objective study.

5. The data at hand do not, as yet, permit final conclusions as to the efficacy of this procedure in selected cases of focal epilepsy. They merely suggest that it may have some merit and indicate the advisability of continued study.

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THE CRANIAL SERIOGRAPH AND ITS UTILITY IN NEUROLOGIC RADIOLOGY FOR CEREBRAL ANGIOGRAPHY

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IN PREVIOUS publications I have described in detail the modern technique employed (or latterly used) for obtaining complete cerebral angiographies. Complete angiography consists of examinations of three roentgenograms—arteriography, phlebography of the first and phlebography of the second phase.

Until recently we have left the technique of taking complete cerebral angiography up to the judgment of the individual examiner. I, at the onset and for some time thereafter, have employed the "escamoteador" conceived by Professor E. Moniz, and without a doubt would have continued to employ it if I had remained at a permanent location or institution. Because of the large size of the escomoteador, its difficulty of transportation precluded its general use. The importance of taking three roentgenograms at intervals of one and one-half seconds between each after the moment of completing the injection, is paramount, because although in many cases the arteriography alone is adequate to establish the diagnosis, frequently phlebography of the first phase or phlebography of the second phase is indispensable to establish an absolute diagnosis as we will see subsequently.

I wish to emphasize again the fact that with a single injection of a radiopaque substance (thorium dioxide or diodrast) it is possible to obtain the three aforementioned plates using our technique and our cranical seriograph. Unfortunately, people still do an incomplete angiographic exploration. In a recent publication of Gross[1] still only arteriography is mentioned.

The model of the "seriograph," which we have been using these past few years and which will be described later, has as its principal characteristics a portable size adaptable to any x-ray table, and a smooth and certain function. This model for cranial angiograms has provided ample proof of its utility, maneuverability, ease of function, and portability during the past five years which I have emphasized in the several clinics in which I have worked recently. The cranial seriograph is constructed to be used with 10 by 12 x-ray film and is made up as a box 15 by 12½ by 4 inches, the inside of which contains vertical springs of steel and a platform of two horizontal frames which articulate at four points, the latter moving freely on the bottom of the case by a system of rounded edges. On this platform are placed three identical trays (cassette carriers) measuring twelve and seven-eighths and fourteen and two-eighth inches, inside of which are placed thin sheets of lead.

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The cassettes are placed over the lead sheets, which should be equipped with reinforced metallic edges.

As the external measurements of the cassette 10 by 12, which are preferred for these purposes, vary according to the particular commercial source, our cranial seriography can be used with any standard cassette, provided there are employed as needed small strips of wood of various sizes to provide immobility of the cassettes in the tray.

Fig. 1.—The cranial seriograph, showing all the different parts of which it is constructed. The cover is formed by a Lysholm grid. The box shows the vertical springs. The movable platform shows the horizontal springs and articulated arms. The tray and cassettes are in position.

The cover of the box has on its superior surface a Lysholm grid protected within by an aluminum plate of the same dimensions. The vertical springs are two inches in height but no longer function when tray No. 1 and its cassette flip out, while the horizontal frames remain functioning, due to the articulated lever, and act on the second and third cassettes. The power of the springs and their action are adjusted in such a form to permit equilibrium and a constant balance between the individual trays with their cassettes, even when they are slipped out one by one.

The cranial seriograph is placed at the extreme end of the x-ray

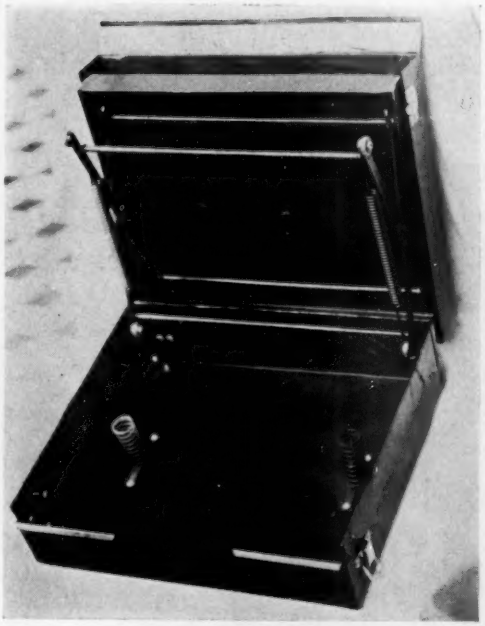

Fig. 2.

Fig. 3.

Fig. 2.—The cranial seriograph showing the combination of springs and cross arms with rollers which provide steady, precise, smooth function.

Fig. 3.—The cranial seriograph loaded and just prior to being closed and placed on the x-ray table. Observe how the trays and cassettes are in perfect equilibrium. The cover can be closed easily without requiring compression.

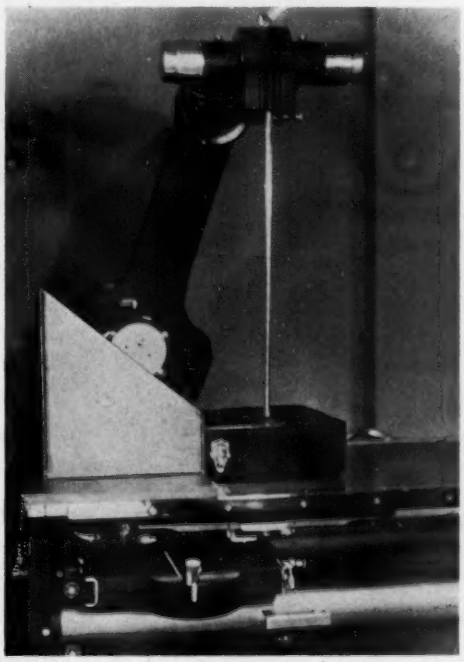

Fig. 4.—The seriograph loaded and in position on the x-ray table, with the tube centered and also the lead protector which prevents the exposed films from further exposure to x-rays.

table and equidistant from each edge, loaded with three cassettes. The end of the apparatus for receiving each exposed cassette is proteced by a lead covering as depicted in Figs. 4 and 5. The x-ray tube is centered at a distance of forty inches so that the central rays pass through the

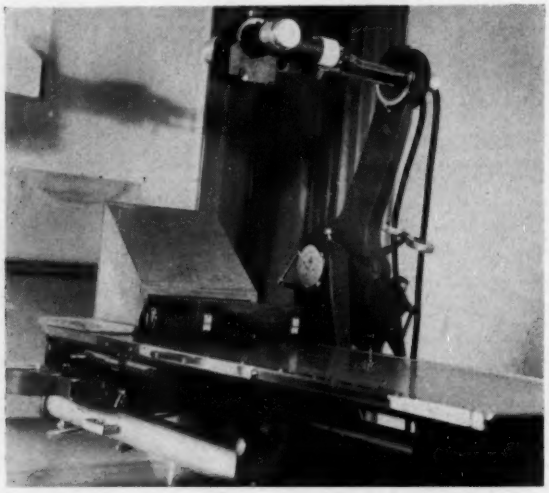

Fig. 5.—Panoramic view of cranial seriograph in position with the tube adjusted and ready for use.

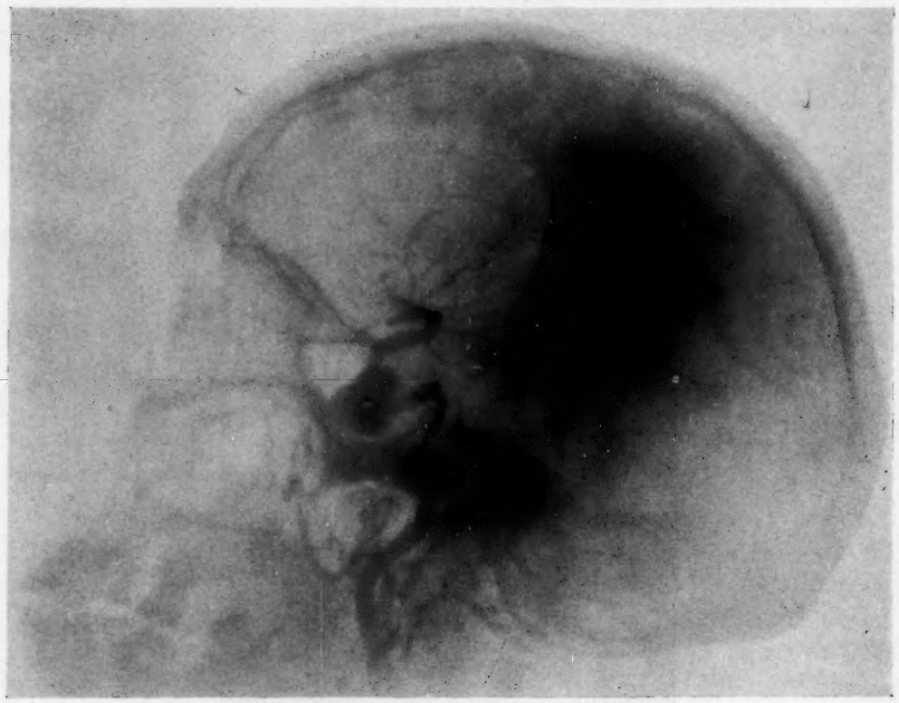

Fig. 6.—Aneurysm of internal carotid. In this case arteriography (first film of the complete angiogram) was sufficient to establish the diagnosis. The phlebograms of first and second phase had a normal appearance.

center of the seriograph, which corresponds with the center of the film. Once this has been done the patient is placed on the table in the supine decubitus position and the patient's head rested on the cranial serialograph so that the side of the head is on the instrument. It is advisable to place a pillow under the shoulder on the side one desires to use for the injection. This facilitates securing the posture sought. A band maintains the head in position. After exposing the common carotid, the injection of 6 c.c. of the radiopaque substance is made (diodrast or thorium dioxide) and at the same instant this has been completed, the initial film is exposed for 0.2 second. This is the arteriogram. The No. 1 tray and its cassette are then slipped out, and remain protected

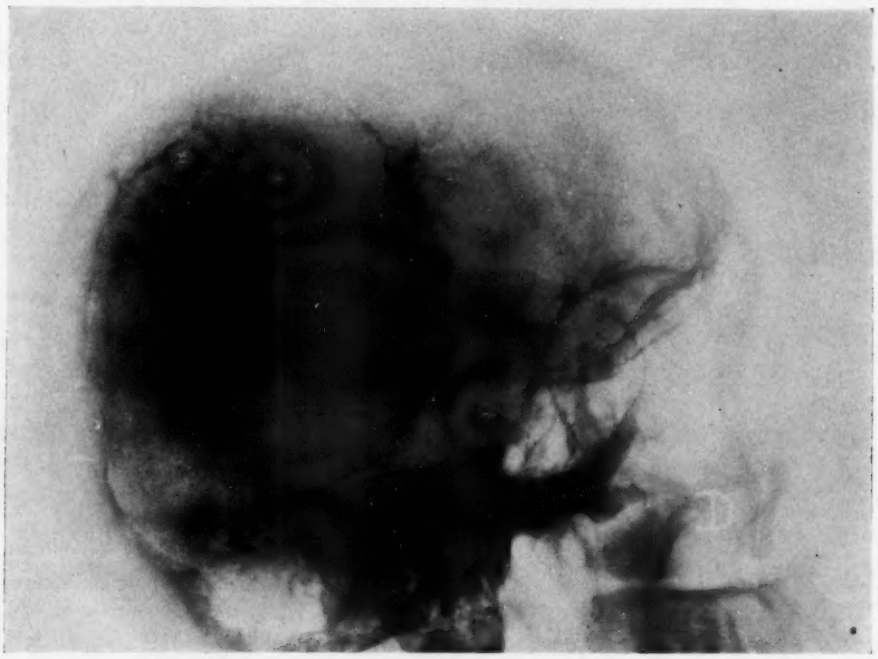

Fig. 7.—Cerebral tumor of posterior part of parietal lobe. In this case the phlebogram of first phase (second film of the complete angiogram) was necessary to establish the diagnosis. The arteriogram and the phlebogram of the second phase had a normal appearance.

by the lead box. After one and one-half seconds have elapsed, the second film is exposed for 0.2 second. This is a phlebogram of the first phase. The No. 2 tray and its cassette is then removed and comes to lie over the No. 1 under the lead protector. After an elapse of an additional one and one-half seconds, the third exposure is taken. This is the phlebogram of the second phase. The third tray is then removed, all are developed, and one has the complete angiogram.

In order to complete this work, I will present three cases which illustrate clearly the necessity of employing complete cerebral angiography in order to obtain a complete exploration.

In the first case one can observe the lesion in the arteriogram phase, the first plate of the complete angiogram. It is a tremendous aneurysm

of the internal carotid. The phlebograms of the first and second phases were normal.

In the second case the angiogram shows an arteriogram difficult to interpret but the phlebogram of the first phase (the second film of the complete angiogram) shows very clearly a shadow corresponding to a cerebral tumor of metastatic carcinoma type, a fact corroborated by

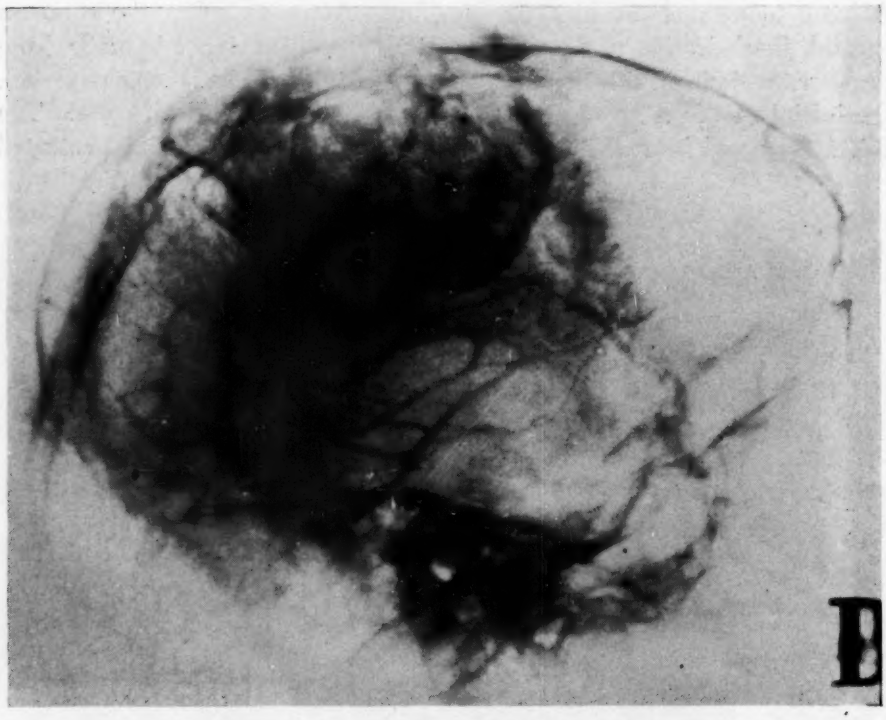

Fig. 8.—Parietal meningioma of the right side. In this case the phlebogram of second phase (third film of complete angiogram) was indispensable to the establishment of the diagnosis. The arteriogram and phlebogram of the first phase were less demonstrative.

necropsy following an operation. This tumor corresponded in size with the one shown in the phlebogram of the first phase. The phlebogram of second phase was essentially normal. The final one of the three cases was one seen on the University neurological service. It was a meningioma. The arteriogram and phlebogram of first phase were both essentially normal, but the phlebogram of the second phase (third film of the complete angiogram) shows very clearly the existence of a very vascular meningeal tumor.

I believe that these cases are sufficiently eloquent to emphasize the importance of obtaining the three phases of cerebral circulation with a single injection of 6 c.c. of radiopaque substance (diodrast or thorium dioxide) and to accomplish by this method a complete angiographic exploration.

Our seriograph makes this object possible and simple.

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THE SUPPRESSION OF INFECTION IN RECENT WOUNDS BY THE USE OF ANTISEPTICS

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I AM well aware that there is a strong group of surgeons who feel that no antiseptic should be used in recent wounds and I understand that this view is held by them because they consider that no antiseptic will kill all the bacteria in a wound and that if any antiseptic is used it will so damage the tissues of the wound that the natural body defense is less able to cope with the remaining organisms than if the antiseptic were not used. In order to refute at once the existence of a general law that bacteria cannot be critically damaged by chemicals without damaging the tissues more, I would point out that the sulfonamides so damage bacteria that they cannot feed themselves and reproduce and are thus rendered an easy prey for the attacking antibacterial forces of the tissues, and penicillin appears to be both bactericidal and harmless to tissues in bactericidal strengths. These examples make it obvious that it is not necessarily hopeless to find a chemical which will damage or destroy bacteria in a wound and still leave the tissues essentially unharmed.

Because there are new antiseptics being offered by the drug houses it seemed desirable to inquire whether any of them presented qualities which would make them more likely to be useful in suppressing infection in wounds than the antiseptics which many surgeons have decided are useless. In war this problem seems particularly important.

An antiseptic to be effective for our purpose should probably possess the following capabilities:

1. In the strength used it should kill germs if diluted at least two to four times more.

2. It should retain most of its germicidal ability in the presence of serum, blood, and crushed tissue, as well as miscellaneous dirt.

3. The essential chemical should not react with the tissue juices or blood and thereby be rendered inert.

4. It should not be a protein coagulant like phenol because on application a scum of coagulum might bridge over microscopic pockets and prevent the deeper penetration of the antiseptic.

5. It should interfere to a minimum with the power of the blood by its leucocytes and the tissues to deal with organisms not killed by the antiseptic.

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6. It would be desirable if the antiseptic could cross cell membranes and kill organisms which had somewhat invaded the tissues. It seems probable that no antiseptic has this power to a useful degree.

7. It should be nonselective toward various bacteria. All the antiseptics to be considered are fairly nonselective but the coal tar derivatives, dettol and amphyl, like phenol show minimum selectivity.

8. The product should be sufficiently inexpensive that one will feel no hesitation in using as much as desired.

9. It should be of proved clinical value.

The following antiseptics were inquired into to see how well they fulfilled the above requirements. (A summary of the study of the literature is here presented, a more complete review of which is given elsewhere.[1]) They are: 1 per cent aqueous iodine (Lugol's solution diluted 5 times), 5 per cent dettol (Dett), ½ per cent amphyl, 1/500 metaphen, 1/3000 furmerane, 1/1000 zephiran, 1/1000 merthiolate, 1/1000 proflavine (and acriflavine and 2:7 diaminoacridine hydrochloride).

The order in which these were named represents roughly their germicidal power in terms of which can be diluted more and still kill bacteria. It is probable that none kill spores in the time they could practically be used in treating a wound. The available data make it impossible to place furmerane, zephiran, metaphen, and merthiolate with exactness.

I shall now consider each of these individually. Since my conclusion is that iodine, furmerane, zephiran, metaphen, and merthiolate do not seem to hold much hope I shall discuss them first.

Iodine 1 per cent (Lugol's solution diluted 5 times) is a powerful germicide in an aqueous medium and can kill germs if diluted about fifty times. However, it combines rather freely with almost any organic material and is largely inactivated by blood. It coagulates proteins and four times greater strength is necessary to kill bacteria than leucocytes in the presence of fifty per cent blood. It is therefore not likely to be a useful antiseptic.

Merthiolate, Metaphen, and Furmerane are organic mercurials and though furmerane has just recently been released* and there is as yet little information available about it, it seems proper to group it with the other two.

In a general way the germicidal activity of the solutions of merthiolate and furmerane recommended for use are about equal while that of metaphen is somewhat greater. Generously regarded, the mercurials can be diluted five to ten times and kill *Staphylococcus aureus* in ten minutes. In passing, mercurochrome "can be condemned on the ground of deficient bactericidal powers alone."[3]

*Released by G. D. Searle & Co., Chicago, Ill.

The mercurials in other ways fall down seriously. They are largely inactivated by the presence of blood and serum. They appear to be highly toxic to tissues and especially to leucocytes. This great tissue toxicity nullifies any values they may have as bacteriostatic agents for the mere temporary checking of growth is of minimum value because if live leucocytes are not promptly forthcoming the organisms soon begin to grow again.

The mercurials then would seem to be unreliable for this purpose.

Zephiran is a nonmercurial antiseptic of somewhat greater germicidal power than merthiolate and metaphen when organic material is absent. It appears to be subject to the same disadvantages as the mercurials. Its potency is tremendously decreased by the presence of blood or serum. It precipitates with serum or laked blood and is the only one which does. It is toxic to leucocytes if diluted to 1/100,000 (i.e. the 1/1000 solution diluted 100 times). It therefore seems that it would be unreliable for our purpose.

Dettol 5 per cent (Dett) is made by diluting to one to twenty dettol as supplied by the manufacturer.* In a 5 per cent solution it has strong germicidal power (i.e. somewhat greater than the mercurials) and this is only moderately decreased by the presence of large amounts of organic matter. The essential chemical is not dissipated by combining with tissue proteins. It does not precipitate proteins. It is almost wholly nontoxic to fixed tissues but is probably toxic to leucocytes. A wound can be soaked for an hour without grossly damaging the tissue. The material is a solution of a synthetically modified cresol. It would seem to be worth considering the use of 5 per cent dettol for application to wounds.

Amphyl† *½ per cent* is a product which is somewhat similar to dettol but has an added ingredient. It is recommended by the maker that it be used in ½ per cent strength and this has less reserve germicidal power than 5 per cent dettol. Until information is available that it can be used successfully in less dilution than ½ per cent strength and until more is known of the toxicity to tissues the 5 per cent dettol should be the preferred product. Amphyl may later, however, be shown to be the equal or superior product and is worth watching.

Acridines (Proflavine, 2:7 diaminoacridine hydrochloride) are more familiarly known as flavines and the best known is acriflavine. Used in 1/1000 solution these chemicals are slow but sure germicides with the ability, about equal to the mercurials, to kill organisms on further dilution if given time for their action. They are bacteriostatic in much weaker dilutions than they are quickly bactericidal. While they do not completely sterilize a culture of organisms quickly, they tremendously reduce the bacterial population in reasonable time and appear to decrease the virulence of the unkilled bacteria, making them more

*It is obtained from Reckitt and Colman Canada Limited, Montreal, or Atlantis Sales Corp., Mustard Street, Rochester, N. Y.

†Offered by Lehn & Fink of Bloomfield, N. J.

susceptible to attack by leucocytes. This point about the bacteriostatic action may be an important difference from that of the mercurials. The germicidal power is not materially influenced by the presence of serum or whole blood. Proflavine and 2:7 diaminoacridine appear to be no more toxic to tissue than normal saline solution, while acriflavine is somewhat toxic. Weak but bactericidal strengths interfere to a minimum degree with the activity of the leucocytes. The flavines have been shown to be of some definite value in preventing infection in experimental wounds in laboratory animals. As acriflavine is slightly more toxic than proflavine and as 2:7 diaminoacridine does not seem to be available in this country, among the flavines proflavine is the one of choice.

SUMMARY

Laboratory considerations would lead to the choice of 5 per cent dettol (Dett) or proflavine sulfate 1/1000 as being antiseptics with some hope of them being useful in suppressing the development of infection in wounds. Dettol (Dett) is a rapid acting germicide not grossly toxic to tissue but probably toxic to leucocytes, while proflavine is a slow acting germicide with great bacteriostatic powers and essentially nontoxic to tissues.

Being unable to find clinical reports in which these substances were given a chance to be effective, I began a clinical experiment to test them out. Lacerations of the hand have the features that: it is particularly desirable to get healing by first intention; they may require burying of suture material to suture tendons or nerves; the amount of soiled tissue which can be sacrificed by débridement is limited, and the blood supply of some of the remaining tissues may be poor. I therefore felt that wounds of the hand would be particularly suitable clinical material for a test. The completed test is to consist in soaking wounded hands in dettol or proflavine for three-fourths hour with the precaution that gross dirt and blood clot are removed and that the antiseptic reaches all parts of the wound. In practice I infiltrate the tissues around the wound putting the needle through sterilized clean skin at a distance from the wound edge, apply a tourniquet to the forearm to completely close the arteries, clip the fingernails short, wash the wound completely free of blood clot and macroscopic dirt using a sterilized brush and dettol solution, then soak the part for forty-five minutes and suture the wound. No débridement is done except where obviously nonviable tissue is present. If the patient does not tolerate the tourniquet well I remove it at about half time and reapply it. I usually scrub out the clot which accumulates from venous oozing two to three times during the soak. So far I have not tried the proflavine; the first cases with dettol were done in August, 1941.*

*I do not expect to be able to complete the experiment in the near future, therefore I felt that the results shown by a limited number of cases should be presented in the hope of interesting others in the matter.

Some hand injuries have not been treated by me in this experiment for I have felt that they were of no use in determining the value or the lack of value of the antiseptic method. The cases which were not accepted as test cases are:

1. Those in which the wound could not be closed, i.e., cases with loss of skin in which surgical judgment indicated that healing by granulation should be allowed. In such cases I could see no way to tell whether the antiseptic was of any value.
2. Superficial wounds which required no suturing. Here there is no question of locking bacteria in the depths and thus the injury is not one in which a judgment could be formed.
3. Puncture wounds. Our antiseptic could not possibly penetrate in these cases and thus if the case healed without infection no credit could be given and if it did not heal no discredit could be given. I have accepted, however, all (which total only a few) of the deep penetrating wounds which had a narrow mouth. The mouth in these tended to close and I had to hold it open during the soak by loose gauze packing. There is some experimental evidence available supporting the contention that the potential infection of puncture wounds can be favorably influenced by infiltration of the track of the wound and surrounding tissues with some of the acridine antiseptics (proflavine, acriflavine, or trypaflavine). I have not, however, observed any of these cases.

The severity of the case has been no bar to their acceptance; in fact, the cases in the series are, on the whole, a little more severe than the average emergency room case requiring suture, for every now and then I would find a case which required suture for which I had not been called and find that the reason I had not been called was that the intern did not think it was a very serious case.

All but three of the cases were treated in the emergency room. It seemed impractical to insist on the elaborate technique of caps, masks, and gowns during the handling of these cases and I am inclined to think that the antiseptic clinging to the cut surface of the wounds is able to deal with any droplet infection which may occur. On this point I feel that these cases have been handled with somewhat less expense in operating room equipment than are those for which a more elaborate operating room set up is maintained. One of our emergency rooms is well equipped while the other, for colored patients, is crowded and poorly equipped. In the summer time in this one we keep a fan blowing on the operating field to keep the flies off! About two-thirds of the patients were treated by interns; some were interested and tried to carry out instructions carefully, some were the opposite.

In all there have been 100 cases. Eighty-six of these wounds healed by primary union in the most rigid sense. By this I mean that there was no pus whatever associated with the wound, there was no redness

or induration of the marginal skin, no soreness and no bead of pus associated with the stitch holes. One more case was wholly as successful except that a little redness occurred in the marginal skin which lasted a few days and then uneventfully subsided. In three cases a bead of pus oozed from one or two stitch holes on removal of the sutures and one of these three had a separation of the wound one-fourth inch long extending through the thickness of the skin but not deeper and the separation healed promptly (this case was not treated until more than twelve hours after the injury and no tourniquet was used). In one case the healing was equally successful except that a silk suture which had been used to suture the flexor tendon of the finger at the terminal interphalangeal joint worked itself out a year after the primary treatment. In two other cases, both of which involved jagged lacerations into the terminal interphalangeal joint, a small amount of pus lay between raised cornified epithelium and the deeper epithelium in the area of one part of the wound. This was found when the wound was dressed for the first time several days after the injury. The deeper part of the wound was healed and after the surface epithelium was trimmed away no further complications occurred in the cases. I am interpreting the situation in these cases as follows: that a blister of serum collected under the cornified epithelium which became infected through the stitch holes after the deeper part of the wound had become effectively sealed off. No deep suppuration occurred and since these wounds opened into the joint it would certainly not be missed if it had occurred. Good movement in the joint in both cases was developing rapidly when last seen. In one other case which required suture five wounds had been inflicted by contact with a powerful electric fan; one-half inch length of one of the wounds gaped open to a depth a little greater than the thickness of the skin on removal of the sutures; this promptly healed by second intention and as this was part of a wound which formed a flap of skin and as no inflammation or pus formation occurred under the flap and there was no inflammation or pus formation at the gaping portion until some days after removal of the sutures it seems likely that infection had been successfully controlled in the case but there remains the question of whether the antiseptic had had some deleterious effect on the healing process. If these eight cases are to be considered as successful from the point of view of prevention of infection—and I think they ought to be so considered—there remains only 6 cases out of the 100 in which infection occurred. None of these cases should necessarily be considered as failures, however, for the treatment planned was not adequately given in essential features. It is even questionable whether they should be included in the series but in the interest of accurate reporting I decided before the treatment was given and the result known whether to include a case in the series or not. To be convincing on the point of whether adequate treatment was given I shall present the following six cases in more detail:

CASE 1.—C. S., in the ninth case in the series, was treated Aug. 27, 1941. The tip of the middle finger had been crushed between the street curb and a heavy wheel. The pulp of the finger was burst on each side. The wounds extended on each side to very near the nail edge. The nail was long and considerable gross dirt was under it. The finger was soaked in the solution for forty-five minutes and the wound sutured. The nail was not clipped short and the gross dirt was not removed from the finger. I am told that a bursting injury of the pulp such as this will show, if examined, that the surface wound communicates by a continuous track of torn tissue with the depths of the pulp. It is not hard for me to imagine that a suction may have followed the bursting which could have sucked bacteria deeply enough into the wound to be beyond the depth of penetration of the antiseptic. Furthermore, with gross dirt left under the fingernail and around the nail it would not be surprising if some were picked up on the suture material, thus contaminating the wound during suturing. (No one expects antiseptics to consistently penetrate gross dirt and kill bacteria in the center of clumps.) The inflammatory process took three days to develop and was never severe.

CASE 2.—T. D., in the fourteenth case in the series, was treated Aug. 28, 1941. There was a jagged nail tear in the left hypothenar area. It was inflicted during a fall while a house was being demolished. The man, during the fall, tried to catch a beam and in doing so caught his hand on the old nail. Penetration was deep and the wound margin tended to fall together. No infections had been seen when this patient came for treatment and I took chances that I ought not to have and which I had specifically planned not to take. This injury was treated by simply immersing the hand in the bath and then suturing the wound. The error in this case was that arrangements were not made for the antiseptic to penetrate to the depths of the wound. I should have applied a tourniquet; then thoroughly removed the blood clot to the furthest depth to which the nail had gone; I should have visualized the pocket and should have seen to it that it did not refill with blood clot. (Looking back I can see that it was absurd to have expected the antiseptic to penetrate anywhere near to the bottom of the laceration in this case and I therefore feel that it should be excluded as a test case.) The infection was not a severe one but was severe enough to require wide opening of the wound.

CASE 3.—A. W. H., in the twenty-ninth case in the series, was treated Oct. 5, 1941. This wound was not soaked for as long a time as usual. It was a laceration one inch long, through the skin on the dorsum of the web of the right hand. The man was in a fight and hit a negro on the face; he thinks his hand hit a tooth. (I did not know the cause of the injury till after the treatment.) There was some tendency to the formation of a flap of skin. Antiseptic solution was squirted over the wound with an asepto syringe for fifteen to eighteen minutes (instead of the forty-five minutes usually used for soaking). A little oozing of blood was occuring and no effort was made to control it. The case subsequently was taken over by another physician who told me that he had to remove a stitch or two but that there was no other trouble and that healing was prompt. Whether a more successful outcome would have been obtained by a more prolonged and more efficient exposure to the antiseptic I cannot say.

CASE 4.—C. S., in the sixty-second case in the series, was treated Jan. 15, 1942. The wound was an inch long, cut by an axe into the extensor side of the metacarpophalangeal joint of the left index finger. The extensor tendon was completely divided and an opening of about one-fourth inch length extended into the joint. There was moderate oozing of blood. I discussed the treatment with one of our interns who had not used dettol before. I asked him to apply a tourniquet on the forearm, to clean out the blood clots with a scrubbing brush, to soak the hand for about five minutes, to irrigate the joint with the fluid for about twenty minutes,

and then further soak the hand for twenty minutes and suture the tendon and skin. I found out later however that he relegated the job to someone else, that a tourniquet was not used (and this seems essential), and that the irrigation into the joint was done for about one and one-fourth minutes (and I am not sure that the joint was properly irrigated for this is not easy to do through a small opening and the rest of the care given appears to have been slothful).

The sutures were removed on the eleventh day and there was no redness, swelling, pain or other evidence of infection. On the twenty-third day, however, the injured joint became sore and on the twenty-sixth day (Feb. 10) pus was oozing out from the joint, with a moderately acute inflammatory process going on. (I note in reports of experiments with laboratory animals that where antiseptics are not completely effective they may delay and minimize the infectious process.)

CASE 5.—S. T., in the ninety-second case in the series, was treated July 14, 1942. An inmate of city jail (because she refused antisyphilitic treatment) cut the palm of her left hand on a broken soft drink bottle. Tendons of two fingers were cut through a skin wound about three-fourths inch long. The case was treated wholly by the interns without supervision. A tourniquet was applied, procaine infiltration of the tissues around the wound was done, and the wound scrubbed out. After soaking for three-fourths of an hour the wound was enlarged proximally to reach the tendons and the suturing done. It is to be pointed out, however, that a wound in the palm, cut with glass deeply enough to sever tendons as in this case and still have a skin opening only three-fourths inch long, is very liable to have the characteristics of a puncture wound in some parts of its depth thus making special care necessary to remove deeply buried bits of blood clot (to allow access of the antiseptic to the depths) and to spread the wound open to allow access of the solution to the depths. In this case a more efficient access of the antiseptic would probably have been obtained by enlarging the wound before soaking rather than after and by suturing the tendons after about twenty minutes' soaking and then continuing another twenty to twenty-five minutes after completion of the tendon suturing, for then the retracted cut ends of the tendon (which must be to a degree contaminated by the injury) are brought down into contact with the antiseptic. Of course, any case with lacerated retracted tendons has to a degree the same difficulties as a puncture wound in having some pockets of the wound inaccessible to the antiseptic.

CASE 6.—A. W., a colored child, aged 8 years, in the one-hundredth case of the series, was treated Sept. 5, 1942. Glass cut the tendons of two fingers in the palm through a skin wound one-half inch long. The motions of the soaking treatment were carried out, namely a tourniquet was used and blood clot was removed from the wound by the use of gauze in forceps but without the use of local anesthetic. The hand was soaked and the suturing carried out. Sulfonamides were used in the wound and given by mouth. I knew nothing of the case until a week after the injury. Infection became evident about the eighth day. This case is similar to Case 5 with a greater degree of the inherent difficulties and errors of treatment. The blood clot could not possibly be removed by the method used in a child of this age and with a deep narrow-mouthed wound such as this without using local anesthetic and without opening the wound; the complication of the presence of blood clot during the soak introduces a factor which really nullifies the case as a test case. If this injury had healed without infection it would not have been included in the series because of having been treated with sulfonamides and statistically I may be wrong in including it.

Four untraceable cases were treated and are not included in the series.

Some injuries in which it would seem to be very difficult to eliminate infection were treated. In some a considerable amount of silk was buried

subcutaneously. A fair number had opened joints. One was a compound fracture, caused by a saw cut through the back of the finger, the finger was attached only by the flexor tendons, vessels and skin; it was sutured back and recovery took place with no infection. When the patient was last seen he seemed to be developing a useful finger. In one case there was a volar flap of skin turned up over the crushed finger tip, the flap was so damaged that it died of dry gangrene but there was no infection or pus associated with it even up to two and one-half weeks when the sutures were removed; the margins of the shrinking flap were stuck by serum to the stump of the finger for the whole time and no pus was present under the dead flap when it was removed.

Eleven compound fractures of the large bones of the limb were treated by the use of the solution (not necessarily soaking). As far as judgment can be based on these I was impressed that the solution has been of help in suppressing infection. Five of them are old enough to indicate that the use of the solution does not interfere with bone healing.

In summary, I present 94 cases treated by this method with 94 primary unions but eight of which had a trivial infection. Six other cases were treated which developed infection but these were not correctly treated in the manner essential to allow efficient access and action of the antiseptic.

A simple attempt was made to get some idea of the bacterial flora in the wounds before and after soaking. For this a small piece of the wound surface (not skin) was put into broth before and after. Eighteen satisfactory before and after cultures were made. All showed growth when taken before the soak. Seven showed no growth after the soak. In some cases two organisms grew before the soak and only one after and in many of the cases which showed growth after, the growth did not come up for several days. Staphylococcus was by far the commonest pathogen and ordinarily it grows up in culture in twenty-four hours.

It is recognized that during the removal of blood clot and debris there is a mechanical removal of bacteria and that this is probably a factor in suppressing infection. I have been unable to devise a legitimate clinical experiment to eliminate this factor.

The purpose of this study was not primarily to develop a method of treating wounds of the hand but to try to find out if antiseptics are of value in suppressing infection of wounds. For this purpose it would seem logical to make wounds in animals and apply various bacteria followed by various antiseptics. This, however, has been amply performed and a summary up to 1922 is given by Neufeld.[2] There is ample proof in this of the value of antiseptics as far as animal experiments go.

I feel that I offer (1) strong reason to suppose that properly chosen antiseptics are of value in suppressing infection in wounds (2) a safe practical method of managing wounds of the hand. I do not say that

the antiseptic used is the best possible and I do not say that the method of application is the most convenient or most efficient possible. By the solution of technical problems it might be possible to make the method of prolonged soaking applicable and of some value in large wounds of other parts of the body. I suspect that those who believe antiseptics are of no value have based their judgment on the observed effects in wounds in which the antiseptic could not be expected to penetrate to all the implanted organisms, e.g., wounds of the last war, or on the observed effects of antiseptics which from laboratory considerations alone would not be expected to suppress the development of infection or on the observed results of clinical trials where the antiseptics were not given a contact with the wound for a sufficient duration of time. I do not wish it to be thought that antiseptics can supplant the removal of gross dirt from a wound or the judicious removal of nonviable tissue. They may supplement such procedures and the sulfonamide drugs may supplement both. It seems to me to be of great importance in any clinical trial that (1) gross dirt and blood clot be removed, and this usually requires a local anesthetic and sterile scrub brush, (2) that bleeding be stopped if possible, because blood clots get into the wound and prevent penetration of the antiseptic, (3) that no pockets are left into which there may be doubt as to the penetration of the antiseptic.

I would ask those who feel firmly that no antiseptic can be of value in suppressing wound infection to note that many injuries occur in factories where a first-aid station is available and that if these wounds were soaked for a little while in a suitable antiseptic and then a compress soaked in the antiseptic were applied for transportation, then the growth of bacteria in the wound would be somewhat checked and the numbers of bacteria in the wound to be dealt with at the final cleansing would surely be much less than otherwise and the hope of primary healing would be correspondingly increased. This would be especially true if the lag period of a couple of hours that bacteria take before growth gets underway is to be passed before the final cleansing is done.

Relative Costs per Gallon Wholesale (128 oz. per gallon = 3.63 litres). —Zephiran 1/1000, $5.00; merthiolate 1/1000, $9.30; metaphen 1/500, $12.50; furmerane 1/3000, $5.95; proflavine 1/1000, $0.58; dett (dettol) 5 per cent, $0.28 (pure dett is $58.80 per dozen gal.); amphyl ½ per cent, $0.01¼ (pure amphyl is $2.50 per gallon).

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CARBAMIDE-SULFONAMIDE MIXTURES IN WOUND THERAPY

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THE advantages of carbamide (urea) in the treatment of infected and contaminated wounds have been detailed elsewhere.[1, 2] The principle of carbamide action is that of a strong peptonizing and lytic agent for devitalized tissues. Carbamide action rids the wound of necrotic tissue by a process of chemical débridement. The action in markedly increasing the rate of healing of infected wounds is on the basis of ridding the wound of deterrents to normal healing rather than by direct bactericidal action. Bacteriostasis results from removing the substances producing bacterial growth and multiplication. Further, this is accomplished without great detriment to the normal physiologic processes of wound repair and without material irritation or damage to normal tissue cells. Excellent results, attested by numerous favorable reports,[3, 4, 5] have followed our revival[1] of carbamide therapy which was first used by Symmers and Kirk.[6] Outstanding as have been the results in the limited field of infected wound therapy, much greater has become the applicability of carbamide in all phases of wound therapy since its combination in topical application with the sulfonamide drugs.[7]

Much has been written and considerable experience has been accumulated on the topical application of the sulfonamides. The bacteriostatic effect of these drugs is the supposed result of a specific interference with the enzymatic utilization by the bacteria of some nutritive chemical factor. The highly selective action of sulfonamides on bacterial metabolism is evidenced by bacteriostasis in the presence of concentrations of these compounds as low as 1 mg. per cent. When implanted directly into wounds these substances, like carbamide, show little demonstrable injury to normal tissue cells or interference with the mechanism of phagocytosis and ultimate tissue repair. The efficacy in the topical use of these compounds in bacteriostasis has been shown to be directly proportional to (1) concentration of sulfonamide inhibitors, (2) solubility and diffusibility, i.e., local concentration of the drugs, and (3) degree of active cellular defense within the wound.

ENHANCEMENT OF SULFONAMIDE ACTION BY CARBAMIDE

Carbamide acts in a number of ways to enhance the action of the sulfonamides. In a preliminary report[7] presenting the results of wound

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therapy with carbamide-sulfonamide mixtures, the removal by the carbamide of gross sulfonamide inhibitors, or the source of such inhibitors, in the form of necrotic tissue, pus, and tissue exudates was stressed. The importance of this chemical débridement must not be minimized either for its direct action or its effect in removing the debris which gives rise to sulfonamide inhibitors. Clark and his co-workers[8] have recently demonstrated that the mere presence of carbamide antagonizes the sulfonamide-inhibitor action of at least one of the end products of protein catabolism. It is probably by antagonizing inhibitors that carbamide enhances the bacteriostatic action of the sulfonamides.

In vitro experiments have shown that ten times as much sulfanilamide is necessary to prevent the growth of a strain of *Escherichia coli* as when the sulfanilamide is used with 5 per cent carbamide. In this concentration the carbamide alone is not particularly bacteriostatic. Similar results were obtained with a strain of *Staphylococcus aureus* using sulfathiazole. Strakosch and associates[9] have reported the same type of results in vivo, using infected dermatoses for their study.

In our earlier study[7] the impression was gained that carbamide increased the solubility of the sulfonamide drugs. This desirable effect would not be an unreasonable result in view of the marked solvent action of aqueous carbamide solutions. Data on this point have been collected as follows.

SOLUBILITY DATA

Temperature, 37.5° C., per 100 Gm. of H_2O:

Carbamide	*Sulfanilamide*
0	1.7 Gm.
20 Gm.	3.5 Gm.
40 Gm.	5.5 Gm.
60 Gm.	8.0 Gm.
100 Gm.	13.5 Gm.

Carbamide	*Sulfathiazole*
0	0.1 Gm.
10 Gm.	0.4 Gm.
30 Gm.	0.5 Gm.
60 Gm.	1.0 Gm.
80 Gm.	1.5 Gm.
100 Gm.	2.0 Gm.

Solubility in a carbamide solution (108 Gm. carbamide in 100 Gm. H_2O) saturated at 20° C.:

20° C. at room temperature	Sulfanilamide	8.5 Gm.
	Sulfathiazole	1.0 Gm.
37.5° C. at body temperature	Sulfanilamide	15.0 Gm. per 100 Gm. H_2O
	Sulfathiazole	2.4 Gm. per 100 Gm. H_2O

Solubility in a carbamide solution (155 Gm. carbamide in 100 Gm. H_2O) saturated at 37.5° C.:

37.5° C. body temperature	Sulfanilamide	27.5 Gm. per 100 Gm. H_2O
	Sulfathiazole	4.0 Gm. per 100 Gm. H_2O

The tremendous increase in the solution of the relatively insoluble sulfa drugs is obvious and the increased concentrations are not obtained by increasing the pH to a high point as in the case with the sodium salts of these compounds. We are of the opinion that this action of carbamide in securing more rapid solution of the sulfa drug used is one of the most important as far as topical application is concerned. This prevents the usual caking of the relatively insoluble sulfa drugs with the attendant foreign-body reaction and interference with the reparative healing process.

The degree of active cellular defense within the wound is aided by carbamide in that this substance sequesters and removes necrotic tissue which is rich in bacterial contamination. It is also probable that the hypertonicity of the solution leads to diapedesis and an increase in the reaction within the wound tissues. Carbamide has been shown by Olson and co-workers[10] to increase the rate of formation of granulation tissue in experimental animals. That it may retard the rate of epithelization[10] in contaminated or infected wounds is of little consequence for epithelial repair is not desired at the time it is used. As soon as the wound is covered with clean granulation tissue treatment with this mixture will have been discontinued.

If carbamide had none of its other known advantages its value as a diluent for the sulfonamides would almost be sufficient reason for its addition to these drugs. The mixture is not only more effective than a sulfonamide alone but is much cheaper. This feature as well as the toxicity limitations in the use of the sulfonamides allows of much greater freedom in the use of the mixture.

PRACTICAL ASPECTS OF THERAPY WITH CARBAMIDE-SULFONAMIDE MIXTURES

Largely from the information gained from the above solubility studies the following mixtures of carbamide (urea) and sulfonamide drugs have been used:

1.	Carbamide	86 per cent
	Sulfanilamide	14 per cent
2.	Carbamide	82 per cent
	Pectin	5 per cent
	Sulfanilamide	13 per cent
3.	Carbamide	80 per cent
	Sulfanilamide	13 per cent
	Sulfathiazole	2 per cent
	Pectin	5 per cent
4.	Carbamide	97.6 per cent
	Sulfathiazole	2.4 per cent
5.	Carbamide	87 per cent
	Sulfanilamide	13 per cent
	Sulfathiazole	2 per cent
6.	Carbamide	89 per cent
	Sulfanilamide	10 per cent
	Sulfathiazole	1 per cent

Mixtures 1, 3, and 5 have been most commonly employed.

No attempt was made to sterilize the crystal mixtures but this would be desirable in wide scale use. Sulfapyridine offered no particular ad-

vantages. Sulfadiazine was also used but it did not appear to have any virtues not possessed by the cheaper drugs. Addition of proportionate amounts of sterile water and warming readily converts the crystalline mixtures into a solution, one or both meeting any practical therapeutic indication.

CLINICAL APPLICATION OF CARBAMIDE-SULFONAMIDE MIXTURES

Use in First Aid.—Carbamide-sulfonamide mixtures (C.S.M.) have been most satisfactorily employed as a first-aid application to contaminated traumatic wounds of all descriptions. The powder is generously sprinkled in all recesses of the wound and the wound covered with sterile gauze secured with an elastic pressure bandage such as a stockinet. The application of this mixture as a first-aid dressing may well prove to be its most important use. When sprinkled over a fresh wound the mixture (C.S.M.) tends to inhibit the growth of bacteria and chemically débride devitalized tissue. In civilian life a contaminated wound is not considered infected until six to twelve hours after the injury, the time depending upon the amount of damage to the tissues. Our experience indicates that with C.S.M. treatment formal surgery may be safely delayed long after twelve hours have elapsed. The rule that compound fractures in civil practice must be operated on within this period may be disregarded in many instances. In the handling of wounds resulting from military action this extended period during which a wound may be kept from becoming infected provides for delay in evacuation of wounded and their transportation to facilities allowing adequate treatment. Also, when large numbers of casualties are brought in at one time the emergency treatment may allow patients to be operated upon in the order of their urgency. It further permits the adequate treatment of shock during this initial period thereby rendering the patient the best possible risk for definitive surgical treatment.

Use in Formal Surgery in Civil Practice.—The primary closure of contaminated wounds, particularly those involving fractures, is a question about which there is some difference of opinion in civil practice. However, it is now the custom of many experienced surgeons.[11] Whether or not it is attempted must depend upon the nature of the wound, facilities, and circumstances as well as the skill of the surgeon. The early treatment of fresh wounds with C.S.M. is a most important factor in making primary closure possible if formal surgery is feasible within a reasonable length of time. Therefore, many contaminated (not infected) wounds may be closed by primary suture without drainage after a careful débridement. Primary healing has been obtained. Following the accepted preparation of the skin and area surrounding contaminated wounds (special care being taken not to introduce irritating and lytic skin antiseptic solutions or even irritating soap solutions into the actual wound) the toilet of the wound itself, before accurate débridement, is accomplished with copious irrigation within a solution of C.S.M.

This is followed by careful débridement (wound excision when possible) and the crystalline mixture of carbamide-sulfonamide is generously dusted into the wound and closure then done with interrupted silk sutures without drainage. Drains, we feel, may introduce further contamination but more particularly are undesirable because they introduce air into any wound producing a fluid level with the inevitable escape of a portion of the rapidly dissolved carbamide-sulfonamide mixture, thereby preventing complete and rapid application of the mixture to all surfaces and recesses of the wound. Soft tissues are sutured as little as practicable, except the skin as noted above. Fractures of the bones are reduced and, if necessary, primary internal fixation is done without fear of complication. Always when possible, regardless of structures involved, immobilization of the part by plaster or compression dressing is employed for greater comfort to the patient and maximum aid to the reparative process. Primary closure of wounds in civil practice may be carried out safely when they are under close observation and when facilities are available for the continued observation of the patient. Primary suture should never be done if thorough débridement and effective wound hygiene cannot be accomplished because of the extent of the injury or lack of time. If infection should develop after closure, the skin sutures may be removed and the wound treated as an open one without fear of any added complication. The results of Ilfeld[12] of this staff, who is reporting a consecutive series of forty-two major contaminated traumatic wounds involving soft tissues, skeletal structures, and joints treated with C.S.M. primarily, followed by careful surgical preparation and débridement with primary interrupted suture of the skin without drainage, are most encouraging. In this series there were less than 3 per cent of wound complications, all of which were minor, and in no instance responsible for further morbidity or complications.

Experience of army surgeons in combat zones has emphasized the necessity for some method of open treatment of wounds as attempts at closed treatment even after formal surgery have generally been unsatisfactory.

Use in Open Wounds.—Wounds in which tissue loss prevents primary closure are treated by the daily application of C.S.M. after suitable surgery including adequate débridement. This is immediately productive of clean, healthy, rapidly growing granulation tissue which permits early successful skin grafting with attendant reduction of disability from scar tissue contraction as well as improvement in the final cosmetic result.

There is a great difference in the ability to get primary healing in civil practice and in battle casualties. War wounds should be left open and in the treatment of these C.S.M. should yield excellent results. A modification of the Orr "closed" treatment has been employed in suitable instances with excellent results. We have modified the original

technique by packing the wound with C.S.M. and covering only the surface of the wound with vaseline gauze before application of closed plaster.

Should an infected wound result because of the impossibility of suitable surgery or any other cause, treatment with C.S.M. yields even better results than the very excellent ones obtained with carbamide (urea) alone.[1, 2, 3] The mixtures are particularly useful in the closed plaster method of treating burns. Stonham[4] has commented on the usefulness of urea alone in this condition.

SUMMARY

Carbamide through a process of chemical débridement has been shown to have many virtues in the treatment of contaminated and infected wounds.

By its combination in topical application with the sulfonamide drugs the applicability of carbamide in wound therapy has been greatly extended. Carbamide removes the source of all and directly antagonizes at least some sulfonamide inhibitors as well as markedly increasing the solubility of the sulfonamide drugs. These factors all contribute to enhancing the efficacy of the sulfonamides.

Wound therapy with carbamide-sulfonamide mixtures is simple and inexpensive; results are excellent. Application as a first-aid measure is most useful in prolonging the period during which it is safe to do definitive surgery.

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THE PATHOGENICITY OF BACTEROIDES MELANINOGENICUS AND ITS IMPORTANCE IN SURGICAL INFECTIONS

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BACTEROIDES melaninogenicus is a small, Gram-negative, anaerobic nonsporulating, black pigment-producing rod which was first isolated in 1921, by Oliver and Wherry[1] from the "throat, tonsils, infected surgical wounds of the abdomen, from urine collected as aseptically as possible, from a suspected focal infection of the kidney and from the feces of a case of chronic dysentery superimposed on an original amoebic infection." Although it was subsequently recovered by Burdon,[2] Varney,[3] Schwarz and Diekmann,[4] Cohen,[5, 6] Liebetruth,[7] and Altemeier[8] from other pathologic processes including pyorrhea alveolaris, pulmonary abscesses, ruptured appendices, peritonitis, the uterus and blood stream in puerperal fever, etc., nevertheless, its role as a pathogen of special interest to surgeons has not been definitely established. According to Bergey and his associates *Manual of Determinative Bacteriology*,[9] it is: "Nonpathogenic for rabbits, guinea pigs and white mice. . . . Inhabits healthy mucous membranes of mammals but may take part in various pathological processes (Burdon)." Likewise, Shevky, Kohl, and Marshall[10] and Liebetruth[7] who continued this work could find no evidence of its invasive capacity. The former remarked, "All attempts to show that *Bact. melaninogenicum* had any significance as a primary or secondary invader in mixed infections gave negative results, so far as clinical evidence or attempts at experimental animal infections could be correlated."

Examination of their protocols reveals that fourteen to eighteen day old cultures were employed by the latter authors for intracutaneous inoculations.[7, 10] Since Burdon[11] has called attention to the fact that old cultures of *Bact. melaninogenicus* may lose their viability, it is not surprising that virulence and invasiveness may, at times, also be lost. Moreover, since we have established the existence of immunologically distinct strains of this organism on the basis of specific proteins,[12] the occurrence of virulent as well as nonvirulent types of *Bact. melaninogenicus* seemed also a likelihood.

From the data of Oliver and Wherry[1] and Burdon[2] as well as from our own observations (Table I) it was tentatively inferred that *Bact. melaninogenicus* is an "opportunist" (in the sense of Theobald Smith) which is capable of producing disease only when given a favorable opportunity to enter the tissues or when the natural resistance to in-

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TABLE I

ISOLATION OF BACTEROIDES MELANINOGENICUS FROM VARIOUS SURGICAL INFECTIONS

	SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
A. Infections of the Respiratory Tract				
1.	M, 67	Subacute inflammation of throat	Biopsy: tissue left pharyngeal wall	Aerobic: *E. coli, Str. viridans, Staph. aureus,* Gram-negative diplococci Anaerobic: *Bact. melan.,* Fusobacteria, diphtheroids, small Gram-negative cocci
2.	F,* 36	Pulmonary abscess; terminal bronchopneumonia	Biopsy: tissue from pulmonary abscess	Anaerobic: *Bact. melan.,* Fusobacteria, Str. (hemol.) *Staph. albus* (hemol.)
3.	M, 42	Bronchiectasis (bilateral)	Sputum	Aerobic: *Str. viridans, K. friendländeri, M. catarrhalis,* diphtheroids, *Staph. albus* Anaerobic: *Bact. melan.,* Fusobacteria, diphtheroids, Gram-negative cocci
4.	F, 29	Lobectomy for bronchiectasis	Pleural fluid	Aerobic: *Staph. albus, E. coli,* Str. (nonhemol.), *Str. viridans* Anaerobic: *Bact. melan.,* diphtheroids, Fusobacteria, gram-negative cocci and small bacilli, *Cl. welchii*
5.	M, 36	Empyema; postpneumonic abscess	Pus from abscess	Anaerobic: *Bact. melan.,* Fusobacteria, *Str. diplococci*
6.	M, 50	None made	Pleural fluid	Anaerobic: *Bact. melan.,* Str. diphtheroids, Fusobacteria, Gram-negative bacilli
B. Infections of the Gastrointestinal Tract				
7.	F,* 52	Appendicitis with gangrene; diffuse peritonitis; diabetes mellitus	Pus from cul-de-sac	Aerobic: *E. coli,* Str. (nonhemol.), Str. viridans Anaerobic: *Bact. melan., Cl. welchii*
8.	F, 52	Perforation of cecum below appendix; ulceration and peritonitis	Pus from abdomen	Aerobic: *E. coli,* Str. (nonhemol.) Anaerobic: *Bact. melan.,* Fusobacteria, *Cl. welchii*
9.	M, 40	Appendical abscess; generalized peritonitis	Pus from abscess	Aerobic: *E. coli,* Str., diphtheroids Anaerobic: *Bact. melan.,* Gram-positive bacilli (nonsporulating), Str. nonhemol.)
10.	M, 54	Ruptured diverticulum with abscess	Pus	Anaerobic: *Bact. melan., E. coli, B. pyocyaneus*

*Died.

TABLE I—CONT'D

	SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
11.	M, 58	Perforated, gangrenous appendix; generalized peritonitis	Pus from abdominal cavity	Aerobic: *E. coli* Anaerobic: *Bact. melan.*, Str., diphtheroids, *Cl. welchii*, Gram-negative coccobacilli, Fusobacteria
12.	F, 27	Acute gangrenous appendicitis with perforation	Abdominal fluid	Aerobic: Gram-negative coccobacilli, *Staph. albus.* Anaerobic: *Bact. melan.*
13.	F, 78	Ruptured appendix; generalized peritonitis	Pus from abdomen	Aerobic: *E. coli*, Str. (nonhemol.), *B. proteus.* Anaerobic: *Bact. melan.*
14.	F, 46	Appendectomy	Pus from abdomen	Aerobic: *E. coli*, Str. (nonhemol.), *B. proteus* Anaerobic: *Bact. melan.*
15.	M, 31	Colostomy and ileostomy	Rectum	Aerobic: *Staph. albus*, Str. (hemol.), *Str. viridans* Anaerobic: *Bact. melan.*, *Cl. welchii*, Gram-negative bacilli
16.	F, 20	Ischiorectal abscess (traumatic)	Rectal abscess	Anaerobic: *Bact. melan.*, diphtheroids
17.	M, 60	Cellulitis of face; tooth infection	Tooth socket	Aerobic: *Str. viridans*, diphtheroids, *Staph. albus* Anaerobic: *Bact. melan.*, Fusobacteria
C. Infections of the Genitourinary Tract				
18.	F, 30	Cesarean section	Vaginal smear	Aerobic: *Str. viridans, A. fecalis, Staph. aureus* Anaerobic: *Bact. melan.*, Str. (nonhemol.)
19.	M,* 62	Diverticuli of bladder; terminal bronchopneumonia; prostatic hypertrophy	Urine	Aerobic: *E. coli*, Str. (nonhemol.), *B. pyocyaneus, B. proteus* Anaerobic: *Bact. melan.*
20.	F, 29	Infected vaginal cyst	Pus from cyst	Anaerobic: *Bact. melan.*, diphtheroids, Fusobacteria, Str.
21.	F,* 19	Perinephric abscess	Pus from abdomen	Anaerobic: *Bact. melan.*, *E. coli* (hemol.), *Staph. aureus* (hemol.), Str. (nonhemol.), *Cl. welchii.*
22.	M, 2½	Pelvic abscess, probably result of ruptured appendix	Pus from colpotomy	Anaerobic: *Bact. melan.*, diphtheroids, *E. coli, Str. viridans*
D. Miscellaneous Infections				
23.	F, 68	Abdominal abscess, iliac region	Pus from abscess	Aerobic: *B. proteus, E. coli*, Str. Anaerobic: *Bact. melan.*, Gram-negative sporebearing bacilli
24.	M, 38	Infection of finger	Pus from finger	Anaerobic: *Bact. melan.*, diphtheroids, Fusobacteria, *Staph. aureus* and *albus, Str. viridans*, Str. (nonhemol.), Gram-negative diplococci

TABLE I—CONT'D

	SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
25.	M, 58	Diabetes mellitus; prepatellar abscess of muscular and fascial tissue about knee and thigh; gangrene of scrotum	Leg stump and amputated leg	Aerobic: *Str. viridans*, Str. (nonhemol.), *Staph. albus*, diphtheroids, *E. coli* Anaerobic: *Bact. melan.*, Fusobacteria, *Cl. welchii*
E. Cultures Taken at Autopsy				
26.	M, 62	Chronic interstitial nephritis; polyposis of stomach; diverticulum of sigmoid; intercurrent bronchopneumonia	Blood	Aerobic: *E. coli*, Str. (nonhemol.) Anaerobic: *Bact. melan.*, Fusobacteria
			Lung	Aerobic: *B. proteus*, Str. Anaerobic: *Bact. melan.*, Fusobacteria
27.	M, 39	Hemangioma of mesentery; necrosis of ileum; peritonitis; septicemia; hydrothorax; hemorrhagic pneumonia; purulent bronchitis	Blood	Aerobic: *E. coli.* Anaerobic: *Bact. melan.*, Str., diphtheroids, *Cl. welchii*
28.	M, 59	Multiple emboli of small pulmonary arteries; pelvic peritonitis; postoperative perineal resection of sigmoid	Blood	Aerobic: *B. proteus, E. coli* Anaerobic: *Bact. melan.*, diphtheroids, Str., *Cl. welchii*
29.	M, 52	Omphalectomy; acute pulmonary infarcts; extensive bronchopneumonia	Lung culture	Aerobic: *Staph. albus, aureus* (hemol.), *E. coli. B. pyocyaneus, Str. viridans* Anaerobic: *Bact. melan., Cl. welchii*
30.	F, 19	Abscess in pouch of Douglas; bronchopneumonia; inflammation of psoas muscle	Pus from right lumbar region	Aerobic: *E. coli, Str. viridans*, Str. (nonhemol.) Anaerobic: *Bact. melan.*, Fusobacteria, diphtheroids
31.	F, 24	Lobectomy for bronchiectasis; serosanguineous pleural effusion; pericardial effusion; gangrene of left upper lobe; thrombosis of hilar veins; lobular pneumonia	Pericardium and lung	Aerobic: *Str. viridans*, Str. (nonhemol.), *E. coli, S. albus, S. aureus* Anaerobic: *Bact. melan.*, diphtheroids, *Cl. welchii*, Gram-negative bacilli
32.	M, 70	Pneumonia with pulmonary abscess	Pulmonary abscess	Aerobic: *Str. viridans* (nonhemol.), *Staph. aureus* Anaerobic: *Bact. melan.*, Fusobacteria, diphtheroids
33.	M, 77	Perforated appendicitis; localized pelvic peritonitis; terminal septicemia with gastric ulcerations and hemorrhage and acute pulmonary thrombosis; chronic cholecystitis and cholelithiasis	Peritoneum	Aerobic: *E. coli*, Str. Anaerobic: *Bact. melan.*, Fusobacteria

TABLE I—CONT'D

	SEX AND AGE	CLINICAL DIAGNOSIS OR AUTOPSY FINDINGS	SOURCE OF MATERIAL	RESULTS OF BACTERIOLOGIC CULTURE
34.	M, 19	Appendicitis; peritonitis; pneumonia	Pus from abdominal cavity	Aerobic: *Staph. albus, E. coli* Anaerobic: *Bact. melan.*, diphtheroids
35.	M, 63	Ileostomy (chronic ulcerative colitis); bowel obstruction	Peritoneal cavity	Aerobic: *B. proteus, E. coli*, Str. Anaerobic: *Bact. melan. Cl. welchii*, Fusobacteria, diphtheroids
36.	F, 55	Carcinoma of rectum; necrosis of pelvic floor; peritonitis	Peritoneal exudate	Aerobic: *B. proteus* Anaerobic: *Bact. melan.*, Fusobacteria, *E. coli, Str.*
37.	F, 65	Gallstones; peritonitis	Peritoneal cavity	Aerobic: *E. coli, Staph. aureus* Anaerobic: *Bact melan., Staph. aureus*, Str. (hemol.), *E. coli*
38.	F, 50	Secondary carcinomatosis following carcinoma of uterus	Pus from peritoneum	Aerobic: *E. coli, B. proteus*, Str., diphtheroids Anaerobic: *Bact. melan., Cl. welchii*, Fusobacteria
39.	M, 69	Perforation of cecum, generalized peritonitis; terminal bronchopneumonia	Peritoneum	Aerobic: Str. (hemol.), *E. coli* Anaerobic: *Bact. melan., Cl. welchii*, Fusobacteria, diphtheroids
40.	F, 32	Hodgkin's disease	Pus from abscess on spine	Aerobic: Gram-positive cocci, Str. Anaerobic: *Bact. melan.*
41.	M, 39	Duodenal ulcer with perforations; generalized peritonitis; recent subtotal gastrectomy and gastrojejunostomy	Peritoneal fluid	Aerobic: Str. (hemol., nonhemol. and viridans), *E. coli, B. pyocyaneus, Staph. albus, Staph. aureus* Anaerobic: *Bact. melan., Cl. welchii*
42.	M, 27	Chronic nephritis; acute enteritis; arteriosclerosis of coronary arteries, aorta, spleen, and adrenals	Fluid in bowel	Aerobic: *Str. viridans, E. coli, Staph. aureus* Anaerobic: *Bact. melan.*, diphtheroids, *Cl. welchii*, Gram-negative cocci
43.	F, 53	Wound infection with extension into subcutaneous tissues of abdomen and thorax; acute peritonitis and adynamic ileus; terminal bronchopneumonia	Sigmoid	Aerobic: *B. proteus, E. coli, Staph. albus*, Str. Anaerobic: *Bact. melan., Cl. welchii*, Fusobacteria
44.	F, 72	Diabetes, left leg amputated; stump infected; bronchopneumonia of left base; edema of lungs	Pus from leg	Aerobic: *B. proteus*, Str. (hemol.) Anaerobic: *Bact melan.*, diphtheroids
45.	M, 45	Perforation of duodenal ulcer; acute peritonitis; bronchopneumonia	Wound culture	Aerobic: *Str. viridans, Staph. albus, Staph. aureus, E. coli* Anaerobic: *Bact. melan.*, Fusobacteria, diphtheroids

fection is abnormally low.[13] We therefore undertook a reinvestigation of its pathogenicity and its role in surgical infections.

EXPERIMENTAL

Use of Freshly Isolated Strains.—Strains of *Bact. melaninogenicus* were isolated from the washed sputums of patients suffering from pulmonary abscess or bronchiectasis. The material was heavily scraped over the surface of several plates of hormone agar enriched with rabbit blood and incubated for four or five days at 37° C. in a Varney anaerobic phosphorus jar.[14] Tubes of Rosenow's glucose brain broth were also used, from which plates were streaked. Colonies were picked under a Zeissler stereoscopic binocular microscope and transplanted to fresh plates of blood agar. In preliminary experiments twenty-five white mice were injected intra-abdominally with three-day old transplants suspended in saline solution or in 5 per cent mucin, prepared according to the technique of Rake.[15] None of the animals died. The bacteria evidently succumbed to the defenses of the peritoneum. We therefore directed our attention to the possibility that this organism may produce only *local* tissue injury or that it needed special protection in order to multiply in the animal's tissues. Mice were inoculated subcutaneously in the groin with 0.05 to 0.1 c.c. of broth cultures. Edema and inflammation which persisted for twenty-four hours or longer were observed at the sites of injection.[12] Control animals injected with heat killed cultures showed no demonstrable lesions.

Five white rabbits were injected intracutaneously on the anterior surface of the hind leg with 0.5 c.c. of a suspension of *Bact. melaninogenicus* made up in cysteine hydrochloride broth. Three of the animals were sacrificed for examination twenty-four hours later. The infected limbs were hot, greenish-black, indurated and swollen to about three times their normal size. Upon removing the skin, the exposed muscles were darker than normal and intensely edematous. An exudate, visible in the subcutaneous tissue near the site of injection, extended all the way up to the axillary region where about 25 c.c. of foul, turbid fluid was present. The muscles of the lower extremities and of the chest wall were likewise discolored, friable, and had a foul odor. The blood vessels were of a very dark hue. The liver, spleen, and kidneys were congested. Cultures of these viscera and of the heart's blood were sterile, but *Bact. melaninogenicus* was isolated in pure culture from the muscles and exudate near the site of injection.

In two other animals of this series, which were sacrificed at the end of forty-eight hours, a pouch of fluid had accumulated in one site and ruptured through a necrotic area in the skin, leaving the muscle exposed. The neighboring lymph nodes were hemorrhagic and a bloody exudate was visible in one of the injected paws. The draining lymph nodes, the heart's blood, and viscera were sterile, but the organism was isolated from the infected muscle and exudate. Three control animals,

inoculated with similar suspensions of heat-killed organisms, presented negative results. In none of the animals was there any evidence of leucocytosis during life.

Effect of Previous Tissue Damage.—In order to test the possible effect of previous tissue damage on the pathogenicity of *Bact. melaninogenicus*, the hair on the backs of rabbits was closely clipped and a standardized dose of staphylococcal toxin (0.02 c.c.) combined with one-fifth of a unit of antitoxin was injected into a series of spots where the culture was inoculated forty-eight hours later. Control injections were made with heat-killed organisms. Inflammation, exudation, and necrosis were observed only where living bacteria were employed.[12] It was concluded that *Bact. melaninogenicus* is capable of producing severe, local tissue injury, especially in areas which had been previously damaged by bacterial toxin.

Effects of Mucin.—Since we recovered *Bact. melaninogenicus* from the respiratory, gastrointestinal, and genitourinary tracts where mucus is usually present (Table I), it seemed desirable to test the possible effect of mucin on its pathogenicity and invasiveness. Previous studies with a variety of other bacteria, including *Neisseria meningitidis*,[16, 17] *Haemophilus pertussis*,[18] *Eberthella typhosus*,[19] *Diplococcus pneumoniae*,[2] *Neisseria gonorrheae*,[21] *H. influenzae*,[22] *Fusiformis*,[23] and *Vibrio cholerae*,[24] have shown that their virulence is markedly increased when suspended in mucin. It has been suggested that mucin supplies the germs with an artificial capsule and interferes with the phagocytic capacity of the leucocytes and the bactericidal action of the animals' serum.[25-27]

Four rabbits were injected intradermally in several spots on the clipped skin of the back with 0.2 c.c. of a suspension made from a strain of *Bact. melaninogenicus* which had been freshly isolated from a rabbit which died after injection with this organism. Comparable sites were inoculated with cultures made up in 5 per cent granular mucin,* adjusted to pH 7.15, according to the technique of Rake.[15] Control areas received either cultures killed by boiling for twenty minutes or with mucin alone. The extent of erythema was noted daily and the edema measured by means of calipers. It was observed that with the use of mucin, there was a very marked increase in the amount of erythema and edema, particularly in the latter. Thus, at the end of forty-eight hours when control areas measured 26 by 36 by 3 mm. the dimensions of those injected with living culture and mucin were two to three times as large. After seventy-two hours, when the controls (without mucin) were essentially negative, the experimental areas still showed marked edema and erythema. One of the rabbits died four days after injection. The entire abdominal wall was black and *Bact. melaninogenicus* was isolated from the underlying muscle wall as well as from the hearts' blood, liver, and spleen.

*We employed granular mucin type 1701-W obtained from the Wilson Laboratories, Chicago, Ill.

Smears made from areas inoculated with mucin and *Bact. melaninogenicus* showed in the Gram stain, a capsulelike substance surrounding the bacilli. This is essentially what has been observed by investigators who worked with other bacteria, as mentioned above.

Presence of Fibrinolysin in Cultures of Bact. melaninogenicus. In previous studies[12] we demonstrated the occurrence of fibrinolysin, a substance which dissolves human blood fibrinogen, in cultures of *Bact. melaninogenicus.* The presence of fibrinolysin is considered by many investigators as evidence of invasiveness or pathogenicity.

SUMMARY

Evidence has been presented that *Bact. melaninogenicus,* a small, Gram-negative, anaerobic, nonsporulating, black pigment-producing germ should be regarded as a pathogen which is of importance in surgical infections.

We have isolated it in combination with other aerobic and anaerobic bacteria from forty-five surgical cases representing various infected wounds, lesions of the pleura and peritoneum as well as of the gastro-intestinal, respiratory, and genitourinary tracts. Others have cultivated it from the blood stream during puerperal infection. At autopsy we found it in the heart's blood, the peritoneum, and visceral organs.

Experimentally, we have shown that it possesses a fibrinolysin which permits it to dissolve human blood fibrinogen, thus interfering with one of the essential defense mechanisms of the inflammatory process, local fixation of microorganisms.[28] In cultures it produces a putrid, foul odor and together with the anaerobic *Str. putrificus* is responsible for the unpleasant odor of some types of pus.[29]

Strains of *Bact. melaninogenicus* were recovered from human lesions, which if inoculated within a few days after cultivation, were pathogenic for rabbits and mice. Intradermal injection produced in the former intense local inflammation, dermonecrosis, and, occasionally, death. Previous damage of the tissue by a bacterial toxin enhances the dermonecrotic properties of the germs. The use of mucin as a menstruum for suspending the bacteria, supplies them with a capsule, thus augmenting their pathogenicity and invasiveness.

Bact. melaninogenicus like *Bact. funduliformis*[30, 31] and certain other members of the genus *Bacteroides,* may therefore be regarded as an "opportunist"[13] which must find conditions suitable for invasion and multiplication.

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EARLY POSTOPERATIVE WALKING

I. The Influence of Exercise on Wound Healing in Rats

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THE controversy relative to the advantages and alleged dangers of early postoperative walking, inaugurated by the publication of Ries's[1] paper in 1899, continues. Since then an evolution in the regimen has resulted in emphasis being placed on getting the patient out of bed and walking within one to twenty-four hours after laparotomy or herniorrhaphy. This change is due to the gradual realization that bed rest, especially in the first few days, is a veritable breeding place for complications.

Although our personal experience in a small clinical series has been successful and the reports of other proponents of the principle of early ambulation have been highly favorable it is obvious that adequate quantitative and objective data should be collected which would definitely indicate the value of the procedure in its various disputed aspects. Fear of wound disruption has been the major deterrent to the acceptance of early postoperative walking. The present report deals with an attempt to determine experimentally the influence of exercise on the rate of healing of standardized laparotomy wounds produced in rats.

EXPERIMENTAL

Method.—Adult male rats were fed on a stock diet. They were kept in glass jars 17 cm. long and 9 cm. in diameter with a wire floor and wood shavings for cleanliness, and a wire face for feeding. They had just enough room to turn around.

Anesthesia was produced by the intraperitoneal injection of 4 mg. of nembutal per 100 Gm. of rat. Epilation was accomplished with a barium sulfide paste. The midline was marked, before draping, with malachite green and under aseptic technique a 5 cm. incision was made in the midline of the abdomen along the raphe extending down from the xiphoid. This was then sutured with Deknatel "moisture proof" C silk in two layers; one interrupted layer including peritoneum, muscle, and fascia with intervals of 5 mm. and taking bites of tissue of about 2 mm.; the other a running stitch of the skin. Knots were triple-throw.

Half of the rats had been trained for two days before operation on a motor-driven treadmill 24 cm. in diameter, revolving 9 r.p.m. After operation these were run for fifteen minutes each day including the day

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of operation and the day of sacrifice. Occasionally the animals, though trained beforehand, hung on the periphery of the treadmill and would fall; it was felt that this simply increased their muscular effort. All, after a few experiences, learned to walk quietly. The controls were kept in their cages except for daily cleaning. The animals in both groups not healing per primam were discarded.

The tensile strength of the wound was determined by a slight modification of the method of Harvey.[2] A one-gallon glass jar was interposed in parallel between a mercury manometer, a compressed air tank and a delivery needle. This served to equalize the rise of pressure. The intraperitoneal needle, after introduction under anesthesia, was moved from side to side and felt with the finger to be free. In spite of this precaution it at times became engaged in retroperitoneal tissue and a generalized emphysema occurred when the air was turned on. To exclude this error the abdominal wall was incised after each reading of tensile strength and the position of the needle, left in situ, noted. When it was found engaged, the results were discarded. The end point was made sharp by sacrificing the animals under water and observing the escape of the first air bubble. The skin almost always gave way before the fascia.

Sections for microscopic study were taken after the animals were sacrificed. The entire abdominal wall was fixed in formaldehyde.

RESULTS

Our data are summarized in Table I and illustrated in Fig. 1.

TABLE I

TENSILE STRENGTH OF STANDARD EXPERIMENTAL LAPAROTOMY INCISIONS

POST-OPERATIVE DAY*	NO.	CONTROL (MEAN RUPTURE POINT MM. HG)	NO.	EXERCISE (MEAN RUPTURE POINT MM. HG)	STANDARD ERROR OF DIFFERENCE
3	11	96.8	10	104.4	11.8
5	15	143.0	14	185.0	12.7
10	12	165.0	11	181.8	11.6

*The day of operation throughout is counted the first post-operative day.

It is apparent that exercise does not adversely affect the wounds of the animals three days postoperatively since statistical analysis reveals the reliability of the difference to be only 0.6. However, on the fifth postoperative day the wounds of the exercised animals are stronger, the reliability of the difference between the groups being 3.3, which is statistically significant. By the tenth day postoperatively this difference disappears and the wounds in both controls and exercised animals are essentially the same (reliability of the difference is 1.4). The table and graph demonstrate further that the tensile strength of the incisions of the exercised animals reaches the maximum in five days while that of the controls requires ten days to attain the same resistance to disruption. This indicates that the wounds of the exercised animals healed more rapidly than did the wounds of the relatively immobilized rats.

DISCUSSION

To our knowledge the only experimental data with reference to the influence of exercise on wound healing are those of Soloman,[3] Mason and Allen,[4] Kimbarovskiy,[5] and Reid.[6] Kimbarovskiy's paper is not accessible. The work of Soloman and of Mason and Allen deals with the special problem of tendon healing which is not germain to our subject. Reid's studies led him to believe that immobilization is a most important factor for primary wound healing. However, under the conditions of our experiments, exercise rather than immobilization seems to be the more valuable.

Our findings confirm the early views as to the stimulating effect of function on healing, which had their inception in the work of Julius Wolff.[7]

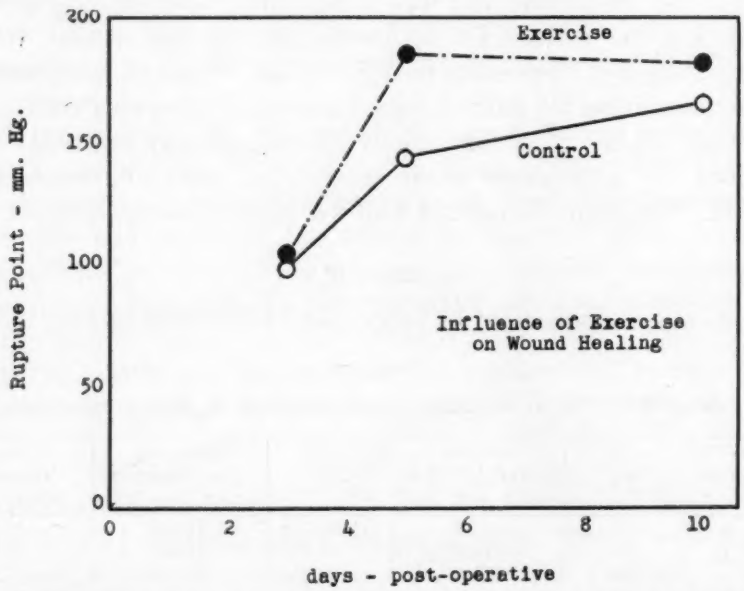

Fig. 1.—Illustrating the influence of exercise on the healing of standard abdominal incisions in rats.

An explanation of the increased tensile strength of the wounds caused by exercise at so early a period as the fifth day must be based on a shortened lag period or, conversely, a more rapid initiation of the period of fibroplasia. There is a latent period of about four days before the growth of fibroblasts becomes appreciable in terms of tensile strength. Howes[8] found new fibrils of collagen within two days in wounds sewn with silk and in three days with catgut. Immature collagen fibers are the only available agent for increasing strength as early as the fifth day. However, study of sections stained both with hematoxylin and eosin and with Masson's stain failed to show any constant variation in fibroblast activity or deposition of collagen between the exercised and unexercised groups.

Two particular items must be considered in the interpretation of our results. First, that the strength of the wound was determined by a relative and not an absolute method, and, second, that the rupture is a weakest-point rupture and so is not dependent on the strength of the sutures but essentially on actual healing of the tissues, and, to some extent, also on the holding power of the tissues for the sutures.

This study suggests that early postoperative walking with its attendant activity is not a factor in the etiology of postoperative wound disruption. In fact, it is even probable that postoperative walking will decrease the incidence of evisceration. However, such a conclusion with reference to man must await detailed analysis of clinical material.

SUMMARY

1. Standardized laparotomy wounds were produced in rats and at intervals of three, five, and ten days, the strength of the wounds was determined in animals which were kept at rest and in others which were exercised.

2. Exercise rather than immobilization was found to hasten the increase in tensile strength of the experimental abdominal incision.

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A STUDY OF THE PHYSICAL FACTORS CONCERNED IN INFLAMMATION

II. Some Factors Which Influence the Spread of Bacteria in Tissues*

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INTRODUCTION

In A preceding communication, certain physical and physicochemical characteristics of inflammation have been defined and quantitated. It was demonstrated that an inflamed focus, whether clinical or reproduced in the laboratory, is the algebraic sum, so to speak, of opposing forces exerted on the two surfaces of the capillary wall. The initial mobilization of these forces is largely due to local chemical stimulation and partly to a reflex. However, the effort of the organism to deflect the activity of the irritant may become so intense and powerful that the irritant actually may be preserved due to the noxious, necrotizing effects of the inflammation itself.

It behooves the surgeon dealing with inflammation to consider the profound effects of elevation and rigid immobilization to reduce swelling, thereby augmenting capillary and venular circulation, and minimizing the spread of bacteria. The favorable results which have been obtained by so treating inflammations of various types attest to the sound physiology governing this method. Realizing that bacterial spread is a corollary of their growth cycle and, therefore, stimulates inflammation, the rates of spread of various bacteria and the factors governing the spread were investigated in the experimental animal.

Character of the Inflammatory Exudate

The Cellular Exudate.—It is impossible to ascertain accurately the origin of the inflammatory cells. The polyvalent reticulum makes it difficult to define the limits of cytopoiesis. Although many authors support the hematogenous origin of cells in the inflammatory field (Baumgarten,[8] Ranvier,[71] and Schridde[81]), there is ample evidence that the local mesenchyme plays a large part in the production of inflammatory cells. Ranvier even spoke of "vasoformative" cells which could produce blood vessels and cells simultaneously—mesenchymal elements lying in the position of the pericytes and which are isolated reservoirs with embryonic potencies.

Although Wharton-Jones[98] distinguished between granular and nongranular white blood cells, Ehrlich[28] first described the use of stains

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to distinguish the cells. The granulocytes, the first leucocytes to arrive on the inflammatory field (Sherrington,[83] Muir,[64] Weiss,[97] Durham,[26] Borrel,[12] Beattie,[9] Bunting,[14] Ewing,[30] and Hardy[47]), have a varied heteroplastic origin: from the blood directly, local and emigrated lymphocytes (Feringa[32]), endothelium (Gerlach and Finkeldey[41]), and the local reticulum (Councilman[18]). The lymphocyte may be of local origin from the reticulum, the macrophages, or directly from the blood. The consensus of opinion is that the lymphocyte has the greatest potentialities of any cell in the inflammatory field, though the monocyte is often credited as being equipotential (Gay and Clark[39]). The monocytes are important, but microorganisms may multiply in their interiors and be disseminated further. Monocytes may originate only from fixed or free histiocytes (Wollenberg,[99] and Shiomi[84]) or from other monocytes (Bloom[11]), but there appears to be a morphologic interchange between the lymphocyte and the monocyte (Paremusoff,[67] and Frumkin[38]).

The histiocytes of normal unaffected regions of the body are stimulated by chemiotactic, hormonal, or autonomic influences so that the normal composition of the blood is altered with the resulting coursing of cells produced in the normal tissues to the area in distress (Sauerbruch,[78] Herzog,[48] Dominici,[23] and Ribbert[76]), but some investigators have doubted the value of this assistance. Maximow[56] has described three great cell types in the inflammatory field: (a) polymorphonuclear leucocytes; (b) polyblasts; and (c) fibroblasts. These categories include all the cell types.

The large phagocytosing macrophages (polyblasts) are (a) hematogenous (Michels and Globus[61]), from the lymphocytes and monocytes, and (b) histogenous, from local fixed or free histiocytes (Ziegler,[100] Foot,[35] Alfejew,[4] and Evans[29]). Adventitial cells (the vasoformative cells of Ranvier) are capable of forming polyblasts (Marchand,[53] and v. Recklinghausen[72]). The following names have been applied to the same cell: macrophage (Metschnikoff[59]), clasmatocyte (Ranvier), vasoformative cell (Ranvier), rhagiocrin cell (Renaut[74]), histiocyte (Aschoff[6]), endothelial leucocyte (Mallory[52]), resting-wandering cell (Maximow), polyblast (Maximow), adventitial cell (Marchand), pyrrhol cell (Goldmann), wandering endothelial phagocyte, or anchored endothelial phagocyte (Cunningham, Doan, and Sabin).

In the inflammatory field are present many cells which seem to be not definite cell types but rather cells which bear the characters of two or more cells. Waldeyer[93] named them plasma cells because of their abundant cytoplasm, but later Unna[91] and v. Marschalko[54] described different cells which they also called plasma cells. According to Downey,[24] plasma cells are of histiocytic origin and are secretory in function.

Fibroblasts are present at the inflammatory focus about the time the monocytes and lymphocytes appear, and are seen to be laying down

fibers even during the active process in an attempt to wall off the septic area. Later they are present in great numbers, laying down heavy meshes of fibrous connective tissue, and comprising nearly the total number of cells in the field. They originate from fixed and free histiocytes (Babkina,[7] and Parker[68]), monocytes, lymphocytes, endothelium (Schaeffer[79]), and other fibroblasts. Maximow, who repeatedly emphasized that fibroblasts are end cells, incapable of further differentiation, was vigorous in his denial of the work of v. Möllendorff[62] who described amitosis of fibroblasts in inflammatory areas to form polyblasts, granulocytes, and nongranular cells. Identical observations were made by Marchand, Siegmund,[85] Weatherford,[95] and Benninghoff.[10] Ebeling[27] maintained that fibroblasts might multiply but never differentiate.

Tissue mast cells arise from nongranular cells (Weill,[96] and Staemmler[87]), but their function is debatable. They may be concerned in the removal of inflammatory debris (Ceelen,[15] and Addison[3]). Perhaps Danchakoff's view[19] that environment, not parentage, of a cell governs its potencies is the most accurate.

The Serous Exudate.—"Associated with these various changes we find increasing pouring of fluid from the tissues along the lymphatics, higher protein content of the discharged fluid and increased cell contents, both leucocytes and, it may be, red corpuscles. Such modified transudate is termed an exudate. In constitution it approaches more nearly to the blood plasma than does congestive edema fluid. It has, however, to be admitted that in different inflammations we find every transition from fluid of one type to the other . . ." (Adami,[2] and Mehu[58]).

Spread of Bacteria in Tissues

Polymorphonuclears secrete a tryptic enzyme, acting in an alkaline medium, which neutralizes the blood serum antienzyme and yields suppuration (softening and eroding) (Opie[66]). Staphylococci, which tend to evoke abscess formation, form a coagulase precipitating fibrin (v. Daranyi,[20] Chapman and associates,[16] Delezenne,[21] Fisher,[33] Gengou,[40] Gratin,[43] Gross,[44] Loeb,[49] Madison,[51] Much,[63] Vanbreuseghem,[92] and Walston[94]). On the other hand, fibrinolytic activity is possessed by hemolytic streptococci (Smith, Hankinson, and Mudge,[86] Tillett and Garner,[89] Pradhan,[69] and Dennis[22]) and pneumococci (Goodner,[42] and Rhoads and Goodner[75]).

Opposing the localizing effects of bacteria is the tendency of fibrinolysis and diffusion known as the spreading factor (Boyland and McClean,[13] Claude,[17] Angevine,[5] Favilli and McClean,[31] and Halban[46]). This spreading factor is present in many normal tissues (McClean,[57] and Duran-Reynals[25]). The tetanus toxin, for example, has an extraordinary ability to diffuse rapidly through tissues. It was formerly believed that the toxin traveled to the central nervous system via the endoneural and perineural lymphatics (Aschoff and Robertson,[6] Fletcher,[34] Friedemann and Elkeles,[36] Fröhlich and Meyer,[37] Gumprecht,[45] Loewi and Meyer,[50] Marie,[55] Meyer and Ransom,[60] and Teale

and Embleton[88]). Following Shdanow's[82] demonstration that no connection existed between the central nervous system and the lymphatics of the peripheral nerves, Abel[1] showed that the toxin was absorbed by the blood and then distributed to the central nervous system.

Statement of the Problem

Since Menkin observed that the local swelling incident to inflammation mechanically isolates the infection and precludes central migration of bacteria, it was planned to determine the blocking effect to strychnine exerted by an inflammatory focus, since the physiologic effect of this drug is so striking.

It has been known that different bacteria possess different faculties of transmitting themselves in tissues (spreading factor); therefore, it was proposed to study the rate of transmission of various common bacteria. The diffusibility of tetanus toxin, which spreads extremely rapidly in tissues, suggested a satisfactory medium for studying the spreading factor of a pure toxin. Following this, the diffusibility of various dyes would be determined and then the bacterial spread defined by staining the injected bacterial suspensions with these dyes.

Because the spreading factor of an organism operates in a manner opposite to the local fixing power of the inflamed area, the degree of fibrinolytic and fibrinogenic power possessed by certain common staphylococci and streptococci warranted investigation.

METHODS AND EXPERIMENTS

Spread of Toxins

Strychnine.—To determine the diffusibility of strychnine sulfate from an inflamed area, 2 white rats, each weighing about 250 Gm., were etherized and the spine transected at the twelfth dorsal vertebra. Then, into a tarsal pad was injected 1.0 c.c. of 5 per cent strychnine sulfate. In a third rat, after transecting the spine, the left leg was immersed in boiling water for 1 minute. Twenty-five hours later, 1.0 c.c. strychnine sulfate was injected into the left tarsal pad. In a fourth rat, under ether anesthesia, the right tarsosural area was circularly burned (using a hot nail), giving a ring-shaped burn. The following day 1.0 c.c. strychnine sulfate was injected into the right tarsal pad. In another etherized rat, the spine was transected at about the tenth dorsal vertebra, and a ring burn made in the skin of the right sural region the following day. Twenty-four hours later, 1.0 c.c. strychnine sulfate was injected into the right tarsal pad. The results of these experiments are given in detail in Table I.

Tetanus.—To determine the rate of absorption of tetanus toxin* from the rat's tail, 31 rats were used. The tetanus toxin was supplied in evacuated vials from which fresh solutions were made. In this series of animals toxin was injected into the tip of the tail and the tail removed

*The tetanus toxin was obtained through the courtesy of Mr. L. T. Clark, of Parke, Davis & Co., annd Dr. E. G. Stewart of Eli Lilly and Company.

TABLE I

DIFFUSIBILITY OF FIVE PER CENT STRYCHNINE SULFATE SOLUTION THROUGH INFLAMED AREAS IN THE RAT

NO.	PROCEDURE	RESULT
a	1 c.c. into tarsal pad	Lethal convulsion 2 min. 20 sec.
b	1 c.c. into tarsal pad	Lethal convulsion 2 min. 20 sec.
c	1 c.c. into heat-inflamed area of leg	No convulsion; survival
d	Ring burn of leg; 1 c.c. into normal distal portion	No convulsion; survival
e	Ring burn of leg; 1 c.c. into normal distal portion	Convulsion 6 min.; death 9 min.

at its base with bone-cutting forceps under ether anesthesia at various intervals. No ligature is necessary after amputation since the bone cutter crushes the caudal vessels sufficiently for hemostasis. In some animals, the survival period after injection of the toxin directly into the heart cavity was compared with that after subcutaneous injection. The results of these experiments are similar to those obtained by Schimmelbusch.[80]

Spread of Bacteria

Nissen[65] found that 5 minutes after injection of hundreds of thousands of *Bacillus anthracis* intravenously in rabbits, negative blood cultures were obtained; however, organisms were recovered from the liver, spleen, and bone marrow. Such is not the case, however, with *B. prodigiosus,* for when cultures of this organism are injected intraperitoneally, intravenously, or intratesticularly into rabbits, the rabbits are dead in 24 hours (Rosahn and Hu[77]). More recently, Reichel[73] found that intravenously injected bacteria were rapidly removed from the blood by antibodies and reticulo-endothelial tissues. Since virulence and invasiveness are different properties (Topley[90]), our experiments were performed with various organisms.

Spread of Bacteria in Normal Tissues.—In this series of experiments, 75 rabbits were used, the general procedure in each case being to make a subcutaneous injection of a bacterial suspension and then to take samples of subcutaneous tissue at definite distances from and including the injection point every four hours thereafter.

Bacterial counts were made in the following manner: The culture, usually on an agar slant, was suspended in sterile broth and diluted until the desired turbidity, as compared with a standard bacterial suspension, was reached; this gave the approximate count. Then, equal amounts of the suspension and blood from finger puncture obtained in a capillary pipette were blown out and mixed on a slide. A smear was then made which was stained with Wright's stain. Twenty-five fields were then counted under the oil immersion, the average erythrocyte count per field and average bacterial count per field being calculated. Then:

$$\frac{\text{Average number bacteria per field}}{\text{Average number erythrocytes per field}} = \frac{x}{5{,}000{,}000}$$

where x is the bacterial count per cubic millimeter. Assuming that the blood contained 5,000,000 erythrocytes per cubic millimeter, 1000x gives the bacterial count per cubic centimeter.

In every case, 0.25 or 0.5 c.c. suspension was injected into the subcutaneous tissues over the tarsosural joint, and samples of subcutaneous tissue taken, usually every four hours, at 0, 3, 6, 9, and 12 cm. above the injection site, 0 referring to the sample taken directly from the injection site. Thus, five samples of subcutaneous tissue were taken from each animal, one rabbit being sacrificed every four hours. Although, in the first experiments, the leg into which the injection was to be made was depilated with barium sulfide prior to the injection, the depilation in latter experiments was deferred until the time of sampling since it was found that barium sulfide produces inflammation of sufficient intensity to cause serious consideration of its blocking effect on bacterial spread.

Sacrifice of the animal having been made by a blow over the occiput, ether or other blood contaminants being avoided because of their questionable effect on bacteria, the extremity of the rabbit was placed on several clean towels so that it was horizontal. An area considerably wider than that to be incised was thoroughly wetted by patting, not rubbing, water into the fur. Then the barium sulfide was sprinkled over the wet area and gently patted down into the hairs, any rubbing being studiously avoided in order to obviate any mechanical spreading effect. After 3 minutes, using clean cloths, the sulfide was wiped off gently from multiple areas, the wiping motion progressing from distal-to-injection site toward the injection site itself. In the same manner, the remainder of the sulfide was washed away with water, and then 70 per cent ethyl alcohol was flushed over the entire field followed by flushing with sterile 0.9 per cent sodium chloride solution.

All instruments having been sterilized, the skin 12 cm. above the injection site was incised and an area of subcutaneous tissue quickly cut away and placed in a sterile Petri dish for culture. The tissues from the 9, 6, 3, and 0 points were taken in the order named in order to avoid any possible contamination that might occur if tissues were taken in the reverse direction.

In the latter experiments, an attempt was made to compare the growth from actual tissue substance in the manner just described with growth from subcutaneous fluid. To obtain this fluid, five previously sterilized tuberculin syringes and No. 25 gauge hypodermic needles were used. Before an incision was made into a designated area for excision of tissues, 2 minims of sterile saline solution were injected subcutaneously into the area and quickly aspirated, rotating the syringe in order to prevent plugging of the needle opening. At best, only a trace of subcutaneous fluid is aspirable, even in distinctly edematous areas. The material so obtained was then quickly squirted into a sterile Petri dish for culture.

In nearly all of these experiments, a specimen from the spleen was cultured as an example of a reticulo-endothelial structure. Experiments (to be described later) showed that intravenous injections of large quantities of bacteria were entirely removed from the blood stream in 15 to 20 minutes. Therefore, in the rabbits injected subcutaneously, no blood cultures were obtained, but the spleen was cultured in order to determine if bacteria which rapidly spread subcutaneously were not also delivered into the blood and removed by the reticulo-endothelium. To obtain spleen specimens, the sacrificed animal was held supine and the skin of the entire abdomen rapidly reflected to each side with a sharp scalpel. Tincture of iodine was then flooded over the skinned abdomen and allowed to act for one to two minutes. Then using sterile instruments, a small incision through the abdominal muscles over the stomach was made, the spleen rapidly delivered into the wound by traction on the gastrosplenic omentum, and a piece cut off and placed in a sterile Petri dish. In order to avoid the bactericidal effect of iodine on any bacteria in the spleen, the instruments used to incise the iodized muscles of the abdomen were always discarded and fresh sterile instruments used to manipulate the spleen.

In the earlier experiments, it was thought advisable to determine the number of colonies grown on the Petri dishes in terms of unit tissue weight. For this purpose, previously weighed Petri dishes were used, the sample from the animal then being placed in a sterile dish and triturated with 5 c.c. sterile 0.9 per cent sodium chloride solution. The supernatant fluid, 1.0 c.c., was then pipetted into a sterile Petri dish for culture. The number of colonies grown $\times 5$ was the total number of colonies per weight of tissues used. Then:

$$\frac{\text{Wt. of tissue (mg.)}}{1000} = \frac{\text{Number of colonies grown/weight of tissue}}{x}$$

where x is the number of colonies per gram of tissue.

The calculation of "number of colonies per gram of tissue" was not done in the latter experiments because (a) the initial tissue weights were too small to permit accurate weight differences in the Petri dishes, and (b) the procedure was considered as inviting contamination.

The samples of subcutaneous tissue, aspirated fluid, or spleen in the Petri dishes were cultured after flooding with agar previously melted at 100° C. and then brought to 35° C. before pouring over the specimen. Where blood agar was used, rabbit heart blood was obtained by aspiration through the anterior chest wall, the area being previously depilated, sterilized with full strength tincture of iodine, and cleared with Richardson's solution. Two large stock rabbits were kept for this purpose (ten pounds and twelve pounds), 40 c.c. of blood being taken at one time from a rabbit. The rabbits were used alternately in order to avoid too severe blood deprivation in a single animal and to allow the pectoral muscles to sterilize the previous needle tract before being used again.

The blood so obtained was always cultured before making the blood agar to be certain of its sterility, any question of contamination resulting in the discarding of the blood.

The specimens were cultured in an incubator at 38° C. and inspected from time to time; when the number of colonies reached the maximum they were counted, using a hand lens to see the more recent pin-point colonies, the number being recorded irrespective of size. The counting was facilitated by marking the Petri dishes with a glass marking pencil, subdividing each into several areas, each of which could be checked off. Usually, the final counts were made at the end of 48 hours after culture. Where the colonies were too numerous to be counted accurately, they were recorded as "innumerable."

In some preliminary experiments, specimens of liver as well as spleen were cultured, but because of bleeding incident to excision of either of these organs with constant contamination of the other by blood, only the spleen was used in succeeding experiments. In each experiment, a control animal injected with saline solution subcutaneously was sacrificed 24 hours after injection and tissue samples were cultured. In nearly every case there was found to be contamination with *Staph. albus* but not other organisms. The organisms used were: *Str. viridans,* 18 rabbits; *Str. hemolyticus,* 12 rabbits; pneumococcus type I, 6 rabbits; *B. prodigiosus,* 6 rabbits; *B. pyocyaneus,* 9 rabbits; *Staph. aureus* (stock; Connaught), 18 rabbits; *B. coli,* 6 rabbits.

Diffusibility of Various Dyes: Pohle[70] pointed out that many properties of dyes are important in determining their diffusibility through the capillary wall. Since we were interested in evaluating the spreading factor in certain bacteria using dyes it was necessary to determine the diffusibility of the dye chosen in our particular experimental animal.

In 5 individual rabbits, intramuscular injections into the thigh were made of 5 c.c. 20 per cent sodium thiosulfate solution, 5 c.c. 2 per cent Congo red, 5 c.c. 2 per cent trypan red, 5 c.c. 2 per cent indigo carmine, and 4 c.c. 2 per cent trypan blue, and samples of heart blood plasma and urine examined at various intervals for the injected substance. The urine was obtained by cystostomy and the blood by cardiac puncture. The sites of injection were also inspected to determine the degree of stain remaining at various intervals.

Since our main experimental animal for evaluating the spreading factor was to be the rat, the rates of diffusion of several dyes were determined in 12 rats. After shaving a small portion of the abdomen, 1 minim of the dye solution was injected subcutaneously on one side and intracutaneously on the other. The dyes used were India ink, 1 per cent Congo red, 1 per cent trypan blue, 1 per cent pontamine sky blue, 1 per cent methylene blue, and 1 per cent indigo carmine. The animals were sacrificed at 12 and 24 hours and after incision of the skin the areas were inspected for diffusion of the dyes.

To determine the difference in rate of spread of the dyes between subcutaneous and intramuscular injection, various dyes were injected intra-

muscularly in 24 mature piebald rats. Into six of them about 0.25 c.c. aqueous 0.8 per cent indigo carmine was injected into the crural muscles on the right. About 0.25 c.c. aqueous 1 per cent pontamine sky blue was injected on the left.

In a second group of 6 animals, 0.25 c.c. 2 per cent aqueous trypan blue was injected on the right and 0.25 c.c. 1 per cent on the left.

In a third group of six rats, about 0.25 c.c. aqueous 5 per cent methylene blue was injected on the right, and about 0.25 c.c. 1 per cent on the left.

In a fourth group of 6 rats, about 0.25 c.c. aqueous 2 per cent Congo red was injected into the crural muscles on the right and about 0.25 c.c. 1 per cent on the left.

One individual from each group was sacrificed by etherization and necropsied at 2, 4, 8, 14, 24, and 48 hours. The injected areas were incised and the density of the stain present was noted.

Spreading Factor of Bacteria: In this comparison nearly 700 rats were used. In general, the procedure consisted of mixing bacterial cultures with various dyes, injecting the colored culture subcutaneously in the rat, and determining the degree of spread from the original injection site at various time intervals thereafter by observing the diffusion of the color. Sterile broth, colored with dye, was used as a control for each type of bacteria. The dyes used were: trypan red, 1 per cent; trypan blue, 1 per cent; indigo carmine, 0.8 per cent; Congo red, 1 per cent; India ink; methylene blue, 1 per cent; and pontamine sky blue, 1 per cent.

The organisms used were: *Staph. albus, Staph. aureus, Str. hemolyticus, B. coli,* pneumococcus type I, *B. pyocyaneus, B. prodigiosus,* and *Cl. welchii.*

The organisms were each cultured in veal-infusion peptone broth. To 14 c.c. of broth culture 0.5 c.c. of dye was added using a tuberculin syringe fitted with a No. 25 gauge hypodermic needle. The bacterial count was made according to the method described. As controls, 0.5 c.c. of dye was added to 14 c.c. of sterile broth. Thus, for each experiment (one organism/type being used for one experiment), fourteen tubes were set up, seven containing broth culture mixed with dyes, and seven containing sterile broth mixed with dyes:

1. Trypan red—culture
2. Trypan blue—culture
3. Pontamine sky blue—culture
4. Indigo carmine—culture
5. India ink—culture
6. Congo red—culture
7. Methylene blue—culture
8. Trypan red—sterile broth
9. Trypan blue—sterile broth
10. Pontamine sky blue—sterile broth
11. Indigo carmine—sterile broth
12. India ink—sterile broth
13. Congo red—sterile broth
14. Methylene blue—sterile broth

From each tube, 0.5 c.c. of mixture was aspirated with a tuberculin syringe fitted with a No. 25 gauge hypodermic needle and injected into five or seven rats in the subcutaneous tissue of the abdomen, the number of rats injected depending upon the times at which they were to be

sacrificed. Thus, if five rats were injected with each numbered mixture above, a total of 5 times 14 or 70 rats would be injected. At the time of sacrifice, one of each number above would be etherized, totaling fourteen etherizations. Thus, if it were intended to study at 2, 6, 12, 24, and 48 hours after the injection, 5 times 14 or 70 rats would be injected, and at the end of each designated time interval, 14 rats would be sacrificed.

At the time of sacrifice, the rat was laid supine, each "culture-dye" rat lying side by side with a control "sterile broth-dye" rat. The skin of the abdomen was slit open with a sharp scissors and reflected to either side. The diffusion and intensity of color of the subcutaneous tissue was examined and each infected rat compared with its control. Intensity of color was noted as 1 to 4, the range being from a trace to very heavy persistence of color. A trace cannot be strictly interpreted as indicating that the bacteria or its toxin had diffused into the rat's body, because a dye may leave a stained bacterium or the adsorbed toxin molecule and diffuse separately. In addition, the degree of diffusion from the original injection site was noted and designated as slightly diffused (s.d.), well diffused (w.d.), or all diffused (a.d.). A slight diffusion would mean a spreading of color just beyond the control diameter; well diffused indicates that nearly the entire abdominal subcutaneous tissue was stained; and all diffused would mean that not only the abdominal subcutaneous tissue was stained but the subcutaneous tissue of the thighs and back.

Action of Bacterial Filtrates on Plasma Clots: Although the work of other observers has demonstrated the presence of plasma coagulating substances in bacterial filtrates on citrated plasma, the following experiments were undertaken with a view of quantitating, if possible, the clotting phenomenon.

In one rabbit, freshly aspirated heart blood was citrated to 0.5 per cent with sodium citrate. The blood then was centrifuged and the plasma retained. The optimum recalcification time with 5 per cent calcium chloride solution was obtained, and 3 c.c. quantities of citrated plasma recalcified; 0.5 c.c. of a 225 million per cubic centimeter of saline suspension of *Staph. aureus* was added to the citrated plasma and the effects on the clot noted.

In another experiment, the staphylococcus suspension was filtered and the filtrate used in place of the whole suspension.

In a third experiment the staphylococcus filtrate was added to citrated plasma.

From an autopsy on a patient who had just expired from a streptococcal pneumonia, a fresh culture of gamma hemolytic streptococci was obtained from the pleural fluid on an agar slant, pure smears being obtained. The organisms were suspended in saline in a concentration of 100 million per cubic centimeter, and 0.5 c.c. of this suspension added to a 3 c.c. recalcified plasma clot. In another experiment 0.5 c.c. of a filtrate of the suspension was added to the reclacified plasma clot. In a

third experiment 0.5 c.c. of the filtrate was added to 3 c.c. of citrated plasma.

RESULTS

Spread of Toxins

Strychnine.—In a group of 5 rats, it was found that if strychnine was injected into normal subcutaneous tissues, lethal convulsions would occur in 2 minutes 20 seconds. If the drug were injected into a heat-inflamed area, the animal survived. If injected below an inflamed area on the leg, the convulsions were either obviated entirely or delayed (Table I).

TABLE II

RATE OF ABSORPTION OF TETANUS TOXIN INJECTED INTO TIP OF RAT'S TAIL AND INTO HEART

NO.	AMT. INJECTED (MG.)	ROUTE OF INJECTION	INTERVAL BEFORE AMPUTATION (IN MIN.)	RESULT
1	.2	Heart	0	Dead in 2 days
2	.2	Heart	0	Dead in 4 days
3	.2	Heart	0	Dead in 2 days
4	.2	Heart	0	Dead in 2 days
5	.4	Heart	0	Dead in 2 days
6	.4	Heart	0	Dead in 2 days
7	.1	Tail	0	Dead in 8 days
8	.1	Tail	Immediate	Survived
9	.1	Tail	30	Dead in 7 days
10	.1	Tail	60	Dead in 5 days
11	.1	Tail	90	Dead in 2 days
12	.2	Tail	0	Dead in 4 days
13	.2	Tail	0	Dead in 2 days
14	.2	Tail	0	Dead in 2 days
15	.2	Tail	0	Dead in 3 days
16	.2	Tail	Immediate	Survived
17	.2	Tail	Immediate	Survived
18	.2	Tail	5	Survived
19	.2	Tail	10	Survived
20	.2	Tail	10	Dead in 5 days
21	.2	Tail	20	Dead in 3 days
22	.2	Tail	20	Survived
23	.2	Tail	30	Dead in 3 days
24	.4	Tail	0	Dead in 2 days
25	.4	Tail	Immediate	Survived
26	.4	Tail	5	Survived
27	.4	Tail	10	Dead in 3 days
28	.4	Tail	20	Dead in 5 days
29	.4	Tail	25	Dead in 3 days
30	.4	Tail	60	Dead in 2 days
31	.4	Tail	90	Dead in 2 days

Tetanus.—Tetanus toxin injected into the heart or tip of the tail in rats is equally lethal, death usually occurring in 2 days. If the tail is amputated within 10 to 20 minutes after the injection into the tip, the animal will survive. Usually the animal will die of tetanus if more than 5 to 10 minutes expires after injection before amputating the tail (Table II).

Spread of Bacteria

Spread of Bacteria in Normal Tissues.—Following subcutaneous injection of bacterial suspensions in rabbits, organisms which spread rapidly (*S. viridans, S. aureus,* pneumococcus type I, and *B. coli*) were also found to an equivalent degree in the spleen. The rates of spread of these organisms are shown in Figs. 1, 2, 3, and 4. Some strains of *Staph. aureus, B. prodigiosus,* and *B. pyocyaneus* injected subcutaneously did not spread to any demonstrable degree as far as the culture technique is able to show. It was found that aspirated fluid in the infected field contained organisms when a great number could be demonstrated in culture of the whole tissue itself (Table III).

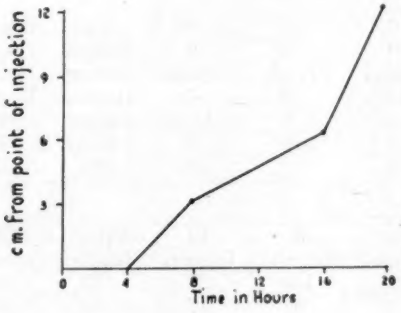

Fig. 1.

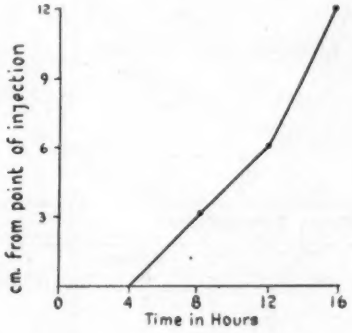

Fig. 2.

Fig. 1.—Rate of *Str. viridans* spread in subcutaneous tissue of the rabbit.
Fig. 2.—Rate of pneumococcus type I spread in subcutaneous tissue of the rabbit.

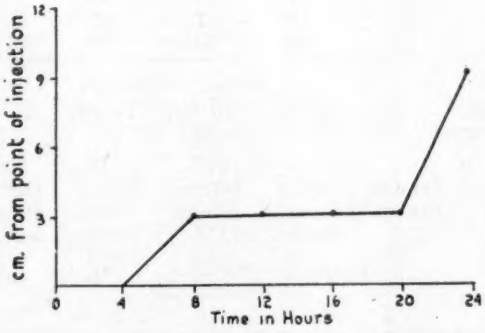

Fig. 3.

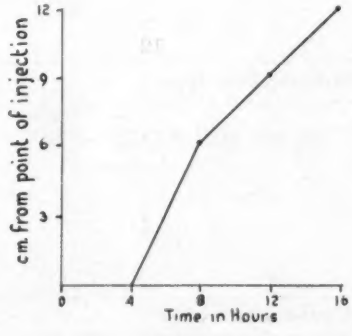

Fig. 4.

Fig. 3.—Rate of *Staph. aureus* spread in subcutaneous tissue of the rabbit.
Fig. 4.—Rate of *B. coli* spread in subcutaneous tissue of rabbit.

Diffusibility of Various Dyes: Congo red, given intramuscularly in rabbits, is found in slight concentrations in the blood and urine. Trypan red, however, injected similarly, is readily found in the blood, and indigo carmine is found in high concentrations in the urine. Trypan blue is rather indiffusible, remaining at the injection site (Table IV).

TABLE III

RATE OF BACTERIAL SPREAD IN RABBITS FOLLOWING SUBCUTANEOUS INJECTION; NUMBER OF COLONIES CULTURED AT VARIOUS DISTANCES FROM SITE OF INJECTION

NO.	NUMBER INJECTED	CM. FROM INJECTION	NO. OF COLONIES AT TIME INDICATED					
A. Strep. viridans:								
			½ HR.	3 HR.	4 HR.	24 HR.		
a	750,000,000	2	132 Gm.	18,333 Gm.	0	—		
b	1,880,000,000	2	1084	—	1084	—		
		4	—	—	—	0		
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.
c	1,950,000,000	Spleen	0	0	0	0	0	0
		Liver	0	0	0	0	0	0
		0	5	Innum.	Innum.	Innum.	Innum.	Innum.
		3, 6, 9, 12	0	0	0	0	0	0
d	1,060,000,000	Spleen	0	0	0	0	Innum.	Innum.
		Liver	0	0	0	0	Innum.	Innum.
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3	0	Innum.	0	4	Innum.	Innum.
		6	0	0	0	Innum.	Innum.	203
		9	0	0	0	0	Innum.	346
		12	0	0	0	0	363	333
B. Strep. hemolyticus:								
a.	775,000,000	Spleen	249	—	50	40	413	100
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3	18	121	100	25	53	45
		6	49	350	61	47	30	50
		9	246	1295	75	30	20	80
		12	70	22	50	16	45	40
			40 MIN.	80 MIN.	120 MIN.	160 MIN.	200 MIN.	4 HR.
b	775,000,000	Spleen	27	27	85	46	25	68
		0	150	107	290	429	58	21
		3	57	52	57	156	17	147
		6	24	30	31	125	24	0
		9	50	36	16	7	51	0
		12	20	40	9	50	96	240
C. Pneumococcus type I:								
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.
a	450,000,000	Liver	—	—	—	88	5	9
		Spleen	—	—	—	297	13	264
		0	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3	0	Innum.	Innum.	Innum.	Innum.	Innum.
		6	0	0	Innum.	1134	Innum.	Innum.
		9	0	0	0	244	12	2
		12	0	0	0	39	0	894
D. B. prodigiosus:								
a	500,000,000	Spleen	0	0	0	0	0	0
		0 (tissue)	38	10	7	17	125	0
		0 (fluid)	18	0	0	2	88	0
		3 (tissue)	0	0	0	0	3	0
		3 (fluid)	0	0	0	0	0	0
		6 (tissue)	0	0	0	0	0	0
		6 (fluid)	0	0	0	0	0	0
		9 (tissue)	0	0	0	0	0	0
		9 (fluid)	0	0	0	0	0	0
		12 (tissue)	0	0	0	0	0	0
		12 (fluid)	0	0	0	0	0	0

Innum. = innumerable.

TABLE III—CONT'D

NO.	NUMBER INJECTED	CM. FROM INJECTION	NO. OF COLONIES AT TIME INDICATED					
E. B.pyocyaneus:								
			4 HR.	8 HR.	12 HR.	16 HR.	20 HR.	24 HR.
a	1,000,000,000	Spleen	0	0	0	0	0	0
		0 (tissue)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		0 (fluid)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3 (tissue)	0	6	10	0	0	0
		3 (fluid)	0	0	Innum.	0	1	6
		6 (tissue)	0	0	0	0	0	8
		6 (fluid)	0	0	0	0	0	0
		9 (tissue)	0	0	0	0	0	0
		9 (fluid)	0	0	0	0	17	0
		12 (tissue)	0	0	1	0	0	0
		12 (fluid)	0	0	0	0	1	0
b	1,000,000,000	Spleen	0	0	—	2	—	0
		0 (tissue)	—	Innum.	—	Innum.	—	Innum.
		0 (fluid)	—	Innum.	—	Innum.	—	Innum.
		3 (tissue)	—	0	—	0	—	Innum.
		3 (fluid)	—	0	—	0	—	Innum.
		6 (tissue)	—	0	—	4	—	2
		6 (fluid)	—	0	—	0	—	0
		9 (tissue)	—	0	—	0	—	8
		9 (fluid)	—	0	—	0	—	0
		12 (tissue)	—	0	—	0	—	0
		12 (fluid)	—	0	—	0	—	0
F. Staph. aureus:								
a	1,650,000,000	Spleen	0	0	0	0	725	0
	(stock)	0	Innum.	Innum.	1	3	563	9
		3	4	28	0	0	26	0
		6	0	21	0	0	0	0
		9	0	0	0	0	0	0
		12	0	50	0	0	0	0
b	5,000,000,000	Spleen	5	16	7	9	0	15
	(Connaught)	0	Innum.	191	Innum.	47	4	156
		3	0	6	6	6	2	3
		6	0	0	0	0	0	4
		9	0	0	0	0	0	12
		12	0	0	0	0	0	1
c	2,665,000,000	Spleen	0	0	0	0	0	0
		0 (tissue)	2	Innum.	Innum.	57	13	5
		0 (fluid)	8	Innum.	Innum.	Innum.	0	1
		3 (tissue)	0	0	0	1	1	0
		3 (fluid)	0	0	3	0	0	0
		6 (tissue)	0	0	0	1	0	0
		6 (fluid)	0	27	0	0	0	0
		9 (tissue)	2	0	0	0	0	0
		9 (fluid)	0	0	0	0	0	0
		12 (tissue)	0	0	0	0	0	0
		12 (fluid)	0	0	0	0	0	0
G. B. Coli:								
a	1,105,000,000	Spleen	0	5	0	14	4	10
		0 (tissue)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		0 (fluid)	Innum.	Innum.	Innum.	Innum.	Innum.	Innum.
		3 (tissue)	0	29	Innum.	12	71	7
		3 (fluid)	0	4	6	0	6	3
		6 (tissue)	0	41	160	5	14	15
		6 (fluid)	0	3	0	15	8	11
		9 (tissue)	0	0	17	21	32	5
		9 (fluid)	0	0	16	3	4	5
		12 (tissue)	0	0	0	23	100	2
		12 (fluid)	0	0	0	1	13	14

TABLE IV

APPEARANCE IN BLOOD AND URINE OF VARIOUS SUBSTANCES INJECTED PARENTERALLY INTO THE RABBIT

NO.	SUBSTANCE	BLOOD	URINE	CONCENTRATION AT INJECTION SITE
a	Sodium thiosulfate	0	0	—
b	Congo red	Slight (4 hr.)	10 min.	—
c	Trypan red	Heavy	Trace	Heavy
d	Indigo carmine	Slight	Heavy	Slight
e	Trypan blue	0	—	—

In rats, pontamine sky blue, Congo red, indigo carmine, and trypan blue diffuse best in the order named, after intracutaneous and subcutaneous injection. India ink was found to be indiffusible. Diffusion of methylene blue similarly injected cannot be evaluated because of the decoloration it undergoes in the tissues (Table V).

TABLE V

DIFFUSIBILITY OF PARENTERALLY INJECTED DYES IN RATS

DYE	12 HOURS		24 HOURS	
	SUBCUT.	INTRACUT.	SUBCUT.	INTRACUT.
Methylene blue	Not well diffused	Not well diffused	Not well diffused	Not well diffused
Pontamine sky blue	Both well diffused	Both well diffused	Both well diffused	Both well diffused
India ink	Poorly diffused	Poorly diffused	Poorly diffused	Poorly diffused
Indigo carmine	No trace	Localized	No trace	Localized
Trypan blue	Slight diffusion	Localized	Well diffused	Localized
Congo red	Well diffused	Well diffused	Well diffused	Well diffused

In a series of 24 rats, it was found that difference of concentration of a dye did not appear to influence its diffusion from an intramuscular injection site. Methylene blue, trypan blue, indigo carmine, and pontamine sky blue diffuse well from such areas (Table VI).

TABLE VI

DIFFUSIBILITY OF DYES INJECTED INTRAMUSCULARLY IN RATS IN DIFFERENT CONCENTRATIONS

TIME OF NECROPSY (IN HR.)	INDIGO CARMINE (.8%)	PONTAMINE SKY BLUE (1%)	TRYPAN BLUE		METHYLENE BLUE		CONGO RED	
			(2%)	(1%)	(5%)	(1%)	(2%)	(1%)
2	3	1	4 Dif.	4 Dif.	4 Dif.	4 Dif.	4 Dif.	4 Dif.
4	Trace	3	4 Dif.	4 Dif.	4 Dif.	4 Dif.	4 Dif.	3 Dif.
8	Faint trace	Trace	4 Dif.	4 Dif.	4 Dif.	4 Dif.	4 Dif.	3 Dif.
14	Absent	Diffusing	4 Dif.	4 Dif.	4 Dif.	3 Dif.	3 Dif.	2 Dif.
24	Absent	Absent	Trace Dif.	1 Dif.	2 Dif.	1 Dif.	3 Dif.	2 Dif.
48	Trace	Absent	1 Dif.	1 Dif.	Trace	Trace	2 to 3 Dif.	1 Dif.

Dif. = diffusing.

Spreading Factor of Bacteria: Bacteria which create severe inflammations (the rat is not subject to severe inflammations) form edematous areas at the subcutaneous injection sites wherein the dye is held. This is true for hemolytic streptococci, *Staph. aureus, B. coli,* and *B. pyocyaneus.* None of the organisms used grow well in the rat. In fact, the rat is quite resistant to any bacterial growth.

Indigo carmine, because of its great diffusibility, is of no value in determining spreading factor by this method. Methylene blue, because of its great diffusibility and greater tendency to become decolorized, should also not be used. Staphylococcus, in particular, exerts a strong decolorizing effect on methylene blue.

All the bacteria used caused the dye to diffuse better than the control broth-dye mixtures. Even the relatively indiffusible India ink diffuses better when mixed with bacterial suspensions. *S. aureus* and *S. albus* have definite spreading factors as tested by this method. *B. pyocyaneus, B. prodigiosus,* and pneumococcus type I show mild spreading factors (at least, in the rat). *Str. hemolyticus* appears to have a strong spreading factor. The Welch bacillus, however, has the most powerful spreading factor of all the organisms used; within 2 hours, the dye-Welch culture has diffused to all parts of the subcutaneous tissue of the rat (Table VII).

Action of Bacterial Filtrates on Plasma Clots: It was found that staphylococcus suspensions contain a fibrinolysin which can partly liquefy a plasma clot in some instances. On the other hand, certain staphylococcus filtrates contain a coagulase which clots citrated plasma (Table VIII, *A*).

Gamma hemolytic streptococcus suspensions liquefied plasma clots. A coagulase is, apparently, first formed by streptococci, and a fibrinolysin is formed later (Table VIII, *B*).

DISCUSSION

The blocking effect on the passage of strychnine past a burned area is largely a mechanical effect due to lymphatic block and coagulation of the intracellular matrix. The drug has a tendency, however, to leak into even the finest channels. This avidity for passage into the circulation is strikingly shown in the tetanus toxin experiments. This toxin is so rapidly absorbed from the tail tip that unless the tail is amputated at the base within 10 or 20 minutes after the injection of toxin into the tip of the tail, the animal will die of tetanus.

Although *Staph. albus* produces an exotoxin and leucocidin (destroying leucocytes), it does not usually have a powerful spreading factor. The staphylococcus may be dermonecrotic, hemolytic, or lethal. The relative production of coagulase or fibrinolysin may determine whether a patient will live with a boil or die of staphylococcemia. Streptococci appear to form a great deal of fibrinolysin, our experiments comparing well with the rapid spread of streptococci in living tissues.

TABLE VII

RATE OF SUBCUTANEOUS SPREAD OF BACTERIA (SPREADING FACTOR) STAINED BY VARIOUS DYES IN RATS

MIXTURE INJECTED	TIME OF EXAMINATION						
	2 HR.	4 HR.	6 HR.	12 HR.	24 HR.	36 HR.	48 HR.
A. Staph. albus:							
Trypan red—culture	4	—	w.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	4	—	s.d.	a.d.	a.d.	—	a.d.
Trypan blue—culture	4	—	2	a.d.	a.d.	—	a.d.
	a.d.	—	w.d.	1	1	—	1
Trypan blue—broth	4	—	4	3	2	—	2
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
Pontamine sky blue—culture	3	—	2	a.d.	a.d.	—	a.d.
	a.d.	—	w.d.	1	1	—	1
Pontamine sky blue—broth	4	—	4	3	1	—	1
	s.d.	—	s.d.	s.d.	a.d.	—	a.d.
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	—	2	1	1	—	1
	s.d.	—	w.d.	a.d.	a.d.	—	a.d.
Congo red—broth	4	—	4	2	2	—	1
	a.d.	—	s.d.	w.d.	w.d.	—	a.d.
India ink—culture	4	—	4	4	4	—	4
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
India ink—broth	4	—	4	4	4	—	4
	s.d.	—	s.d.	s.d.	s.d.	—	s.d.
Methylene blue—culture	(Methylene blue oxidized to leuco base by staphylococcus culture after one-half hour contact)						
Methylene blue—broth	4	—	3	2	1	—	0
	w.d.	—	w.d.	w.d.	a.d.	—	0
B. Staph. aureus:							
Trypan red—culture	2	—	1	1	1	—	1
	w.d.	—	a.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	4	—	1	1	1	—	1
	s.d.	—	w.d.	a.d.	a.d.	—	a.d.
Trypan blue—culture	2	—	1	1	1	—	1
	w.d.	—	w.d.	a.d.	a.d.	—	a.d.
Trypan red—broth	3	—	3	1	1	—	1
	s.d.	—	s.d.	a.d.	a.d.	—	a.d.
Pontamine sky blue—culture	2	—	1	1	1	—	0
	w.d.	—	w.d.	a.d.	a.d.	—	—
Pontamine sky blue—broth	4	—	3	2	1	—	0
	s.d.	—	s.d.	s.d.	w.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	—	1	1	1	—	1
	s.d.	—	a.d.	a.d.	a.d.	—	a.d.
Congo red—broth	4	4	1	1	1	—	—
	s.d.	s.d.	w.d.	a.d.	a.d.	—	—
India ink—culture	4	3	3	2	2	—	—
	s.d.	s.d.	s.d.	s.d.	s.d.	—	—
India ink—broth	4	4	3	3	2	—	—
	s.d.	s.d.	s.d.	s.d.	s.d.	—	—
Methylene blue—culture	4	3	2	1	0	—	—
	s.d.	s.d.	s.d.	w.d.	—	—	—
Methylene blue—broth	4	4	3	1	0	—	—
	s.d.	s.d.	s.d.	w.d.	—	—	—

TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION						
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.	4 DAYS	5 DAYS
C. Str. hemolyticus:							
Trypan blue—culture	4 w.d.	4 w.d.	3 a.d.	1 a.d.	1 a.d.	0 —	0 —
Trypan blue—broth	4 s.d.	4 s.d.	3 w.d.	1 s.d.	1 a.d.	0 —	0 —
Pontamine sky blue—culture	4 s.d.	2 s.d.	2 w.d.	1 a.d.	1 a.d.	— —	— —
Pontamine sky blue—broth	4 s.d.	2 s.d.	2 s.d.	1 a.d.	1 a.d.	1 a.d.	1 a.d.
Congo red—culture	4 s.d.	2 w.d.	2 w.d.	2 w.d.	1 a.d.	0 a.d.	0 —
Congo red—broth	4 s.d.	4 s.d.	2 w.d.	2 w.d.	1 a.d.	1 a.d.	0 —
India ink—culture	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 s.d.
India ink—broth	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 s.d.
Methylene blue—culture	4 s.d.	4 s.d.	4 w.d.	4 w.d.	2 w.d.	1 w.d.	1 w.d.
Methylene blue—broth	4 s.d.	4 s.d.	4 s.d.	1 s.d.	1 s.d.	1 w.d.	1 w.d.
D. B. coli:							
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.		
Trypan red—culture	4 s.d.	2 s.d.	2 a.d.	2 a.d.	2 —		
Trypan red—broth	4 s.d.	2 s.d.	2 s.d.	2 w.d.	1 w.d.		
Trypan blue—culture	4 s.d.	4 s.d.	2 s.d.	1 s.d.	0 —		
Trypan blue—broth	4 s.d.	4 s.d.	2 s.d.	1 s.d.	— —		
Pontamine sky blue—culture	4 s.d.	4 w.d.	3 w.d.	1 s.d.	1 w.d.		
Pontamine sky blue—broth	4 s.d.	4 s.d.	3 w.d.	0 —	1 —		
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.		
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.		
Congo red—culture	4 s.d.	4 s.d.	3 s.d.	2 s.d.	2 s.d.		
Congo red—broth	4 s.d.	4 s.d.	3 s.d.	1 s.d.	1 s.d.		
India ink—culture	4 s.d.	3 s.d.	1 s.d.	1 s.d.	1 s.d.		
India ink—broth	4 s.d.	2 s.d.	2 s.d.	1 s.d.	1 s.d.		
Methylene blue—culture	trace	trace	trace	trace	0		
Methylene blue—broth	2	trace	trace	trace	0		
E. Pneumococcus type 1:							
Trypan red—culture	4 s.d.	3 s.d.	3 s.d.	2 w.d.	1 w.d.		
Trypan red—broth	4 s.d.	3 s.d.	3 s.d.	2 s.d.	1 w.d.		
Trypan blue—culture	4 s.d.	2 s.d.	2 s.d.	2 w.d.	1 w.d.		
Trypan blue—broth	4 s.d.	2 s.d.	2 s.d.	2 s.d.	1 w.d.		
Pontamine sky blue—culture	4 s.d.	— —	3 s.d.	1 s.d.	1 s.d.		

TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION				
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.
E. Pneumococcus type I:					
Pontamine sky blue—broth	4	—	3	trace	trace
	s.d.	—	s.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	3	3	2	1
	s.d.	s.d.	w.d.	w.d.	w.d.
Congo red—broth	4	3	3	2	1
	s.d.	s.d.	s.d.	s.d.	w.d.
India ink—culture	4	4	3	—	3
	s.d.	s.d.	s.d.	—	s.d.
India ink—broth	4	4	3	—	3
	s.d.	s.d.	s.d.	—	s.d.
Methylene blue—culture	4	1	trace	0	0
	s.d.	w.d.	—	—	—
Methylene blue—broth	4	3	3	trace	0
	s.d.	s.d.	s.d.	—	—
F. B. pyocyaneus:					
Trypan red—culture	4	4	1	0	0
	s.d.	s.d.	a.d.	a.d.	a.d.
Trypan red—broth	4	4	1	1	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Trypan blue—culture	4	4	1	1	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Trypan blue—broth	4	4	1	1	0
	s.d.	s.d.	w.d.	w.d.	a.d.
Pontamine sky blue—culture	4	4	1	1	1
	s.d.	s.d.	a.d.	w.d.	a.d.
Pontamine sky blue—broth	4	4	1	1	0
	s.d.	s.d.	w.d.	w.d.	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	4	4	3	1	1
	s.d.	s.d.	s.d.	w.d.	w.d.
Congo red—broth	4	4	3	1	1
	s.d.	s.d.	s.d.	w.d.	w.d.
India ink—culture	4	4	3	2	2
	s.d.	s.d.	w.d.	w.d.	w.d.
India ink—broth	4	4	3	3	2
	s.d.	s.d.	s.d.	s.d.	s.d.
Methylene blue—culture	2	0	0	0	0
	s.d.	—	—	—	—
Methylene blue—broth	2	trace	0	0	0
	s.d.	—	—	—	—
G. B. prodigiosus:					
Trypan red—culture	4	3	3	2	2
	s.d.	w.d.	s.d.	s.d.	s.d.
Trypan red—broth	4	3	3	2	2
	s.d.	w.d.	w.d.	s.d.	s.d.
Trypan blue—culture	4	3	3	2	2
	s.d.	s.d.	s.d.	a.d.	a.d.
Trypan blue—broth	4	3	3	trace	trace
	s.d.	s.d.	w.d.	—	—
Pontamine sky blue—culture	4	4	trace	trace	0
	s.d.	s.d.	—	—	—
Pontamine sky blue—broth	4	4	3	trace	trace
	s.d.	s.d.	w.d.	—	—
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.

TABLE VII—CONT'D

MIXTURE INJECTED	TIME OF EXAMINATION				
	2 HR.	6 HR.	12 HR.	24 HR.	48 HR.
G. B. prodigiosus:					
Congo red—culture	4 s.d.	4 s.d.	3 w.d.	trace —	trace —
Congo red—broth	4 s.d.	4 s.d.	3 w.d.	trace —	trace —
India ink—culture	4 w.d.	4 w.d.	trace —	trace —	trace —
India ink—broth	4 s.d.	4 s.d.	3 s.d.	3 s.d.	3 s.d.
Methylene blue—culture	3 s.d.	trace —	trace —	trace —	0 —
Methylene blue—broth	4 s.d.	4 s.d.	0 —	0 —	0 —
H. Cl. welchii:					
Trypan red—culture	2 a.d.	1 a.d.	1 a.d.	1 a.d.	0 —
Trypan red—broth	4 s.d.	4 s.d.	3 w.d.	2 w.d.	0 —
Trypan blue—culture	2 a.d.	2 a.d.	1 a.d.	0 —	0 —
Trypan blue—broth	4 a.d.	4 w.d.	3 w.d.	3 w.d.	2 w.d.
Pontamine sky blue—culture	2 a.d.	2 w.d.	trace —	0 —	0 —
Pontamine sky blue—broth	4 s.d.	4 s.d.	3 s.d.	2 w.d.	0 —
Indigo carmine—culture	n.d.	n.d.	n.d.	n.d.	n.d.
Indigo carmine—broth	n.d.	n.d.	n.d.	n.d.	n.d.
Congo red—culture	1 a.d.	1 a.d.	1 a.d.	1 a.d.	0 —
Congo red—broth	4 s.d.	4 s.d.	3 s.d.	2 w.d.	trace —
India ink—culture	4 s.d.	4 s.d.	3 s.d.	3 s.d.	3 w.d.
India ink—broth	4 s.d.	4 s.d.	4 s.d.	3 s.d.	3 s.d.
Methylene blue—culture	0	trace	0	trace	trace
Methylene blue—broth	trace	trace	trace	trace	trace

1 = slight coloration.
4 = heavy coloration.
s.d. = slight diffusion of dye.
w.d. = well diffused; dye diffused nearly all over abdominal subcutaneous tissue.
a.d. = all diffused; dye diffused over subcutaneous tissue of entire body.
n.d. = no trace of dye visible at two hours.

CONCLUSIONS

1. Tetanus toxin has a spreading factor so powerful that sufficient quantity for lethal issue may diffuse into the general circulation in 10 to 20 minutes after subcutaneous injection.

2. In the rabbit, *S. viridans, S. aureus,* pneumococcus type I, and *B. coli* spread rapidly, while *B. prodigiosus* and *B. pyocyaneus* and some strains of *S. aureus* spread slowly in the subcutaneous tissues.

3. Congo red, trypan red, indigo carmine, and trypan blue diffuse best in the order named in the rabbit. In rats, the order is maintained; however, pontamine sky blue is most diffusible and India ink least diffusible.

TABLE VIII

EFFECT OF BACTERIAL FILTRATES ON RABBIT PLASMA CLOTS AND CITRATED PLASMA

NO.	MIXTURE	RESULT
A. Staphylococcus filtrate:		
a	Optimum recalcification time	3 min. 45 sec.
b	3 c.c. recalcified plasma	Remained clotted 2 days
c	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted 2 days except for serum exudation
d	3 c.c. recalcified plasma plus 0.5 c.c. staphylococcus suspension	Partial dissolution of clot in 48 hr.
e	Optimum recalcification time	3 min. 55 sec.
f	3 c.c. recalcified plasma	Remained clotted 2 days
g	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted
h	3 c.c. recalcified plasma plus 0.5 c.c. staphylococcus filtrate	Remained clotted
i	Optimum recalcification time	3 min. 45 sec.
j	3 c.c. recalcified plasma	Remained clotted 2 days
k	3 c.c. citrated plasma	Remained unclotted 2 days
l	3 c.c. citrated plasma plus 0.5 c.c. staphylococcus filtrate	Firm clot in 7 hr.
m	3 c.c. citrated plasma plus 0.5 c.c. saline solution	Remained unclotted 2 days
B. Streptococcus filtrate:		
a	Optimum recalcification time	4 min. 10 sec.
b	3 c.c. recalcified plasma	Remained clotted 2 days
c	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted
d	3 c.c. recalcified plasma plus 0.5 c.c. streptococcus suspension	Dissolving of clot in 14 to 16 hr.
e	Optimum recalcification time	5 min. 33 sec.
f	3 c.c. recalcified plasma	Remained clotted 2 days
g	3 c.c. recalcified plasma plus 0.5 c.c. saline solution	Remained clotted 2 days
h	3 c.c. recalcified plasma plus 0.5 c.c. streptococcus filtrate	Dissolved clot in 7 to 8 hr.
i	Optimum recalcification time	4 min. 10 sec.
j	3 c.c. recalcified plasma	Remained clotted 2 days
k	3 c.c. citrated plasma	Remained unclotted 2 days
l	3 c.c. citrated plasma plus 0.5 c.c. saline solution	Remained unclotted 2 days
m	3 c.c. citrated plasma plus 0.5 c.c. streptococcus filtrate	Partial clot in 10 to 12 hours with complete dissolution of clot so formed in 48 hr.

4. In the rat, determined by the dye method, *S. aureus, S. albus, S. hemolyticus, B. pyocyaneus, B. prodigiosus,* and pneumococcus type I have mild spreading factors, the most powerful being *Cl. welchii.*

5. The staphylococcus and streptococcus both produce a fibrinolysin and a coagulase, as tested on plasma clots and citrated plasma.

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AN ANALYSIS OF THE REACTION OF THE HUMAN GALL BLADDER AND SPHINCTER OF ODDI TO MAGNESIUM SULFATE

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SOME time ago, the senior author in collaboration with C. L. Birch[1] demonstrated that several hydragogue cathartics (especially $MgSO_4$, Na_2SO_4, and $MgCl_2$) caused marked reduction in the volume of the human gall bladder, as calculated from cholecystograms, and that this loss in volume could be correlated with the appearance of "B" bile in the aspirated contents of the duodenum. At that time no method had been employed for measuring with equal accuracy the decrease in resistance of the human sphincter. Recently, however, Bergh and Layne[2] have obtained manometer readings of the reaction of the sphincter to $MgSO_4$ by utilizing the now common postoperative procedure of draining ducts of choledochostomized patients with T tubes. These detailed measurements make possible, for the first time, a more discriminating analysis of the relative reaction of the gall bladder and sphincter to substances introduced into the duodenum. Accordingly, it has seemed desirable to restudy the effect of $MgSO_4$ upon the gall bladder in a sufficiently large number of individuals to make comparisons with the sphincter studies significant.

With this object in view eighteen medical students, responding to a call for volunteers, were subjected to the usual routine of oral cholecystography. In fourteen individuals the preliminary films showed sufficiently strong gall bladder shadows to be traced. After a Rehfuss tube had been passed, a roentgenogram was made, and then 30 c.c. of a saturated solution of $MgSO_4$ were injected into the duodenum (ten students) or into the stomach (four students, subjects in whom the tube could not be passed beyond the pylorus in the time available). Thereupon roentgenograms were made at 2, 4, 8, 12, 16, 20, 25, 30, 35, 40, and 45 minutes after the injections. Subsequently, the gall bladder shadows were traced, the changing volumes computed in accordance with the method previously described,[3] and the individual curves of evacuation plotted (Fig. 1). Finally, the percentage loss in volume was calculated (Table I) and the mean values plotted (see heavy solid line, Fig. 2) and compared with the mean curves obtained in earlier studies of the reaction of the gall bladder to egg yolk (see heavy dash line, one egg yolk by duodenal tube; light dash line, five yolks by mouth).

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OBSERVATIONS

A comparison of these mean curves of evacuation of the gall bladder, as plotted in Fig. 2, leaves no doubt but that $MgSO_4$ induces emptying of the gall bladder. However, it is much less effective than egg yolk, since

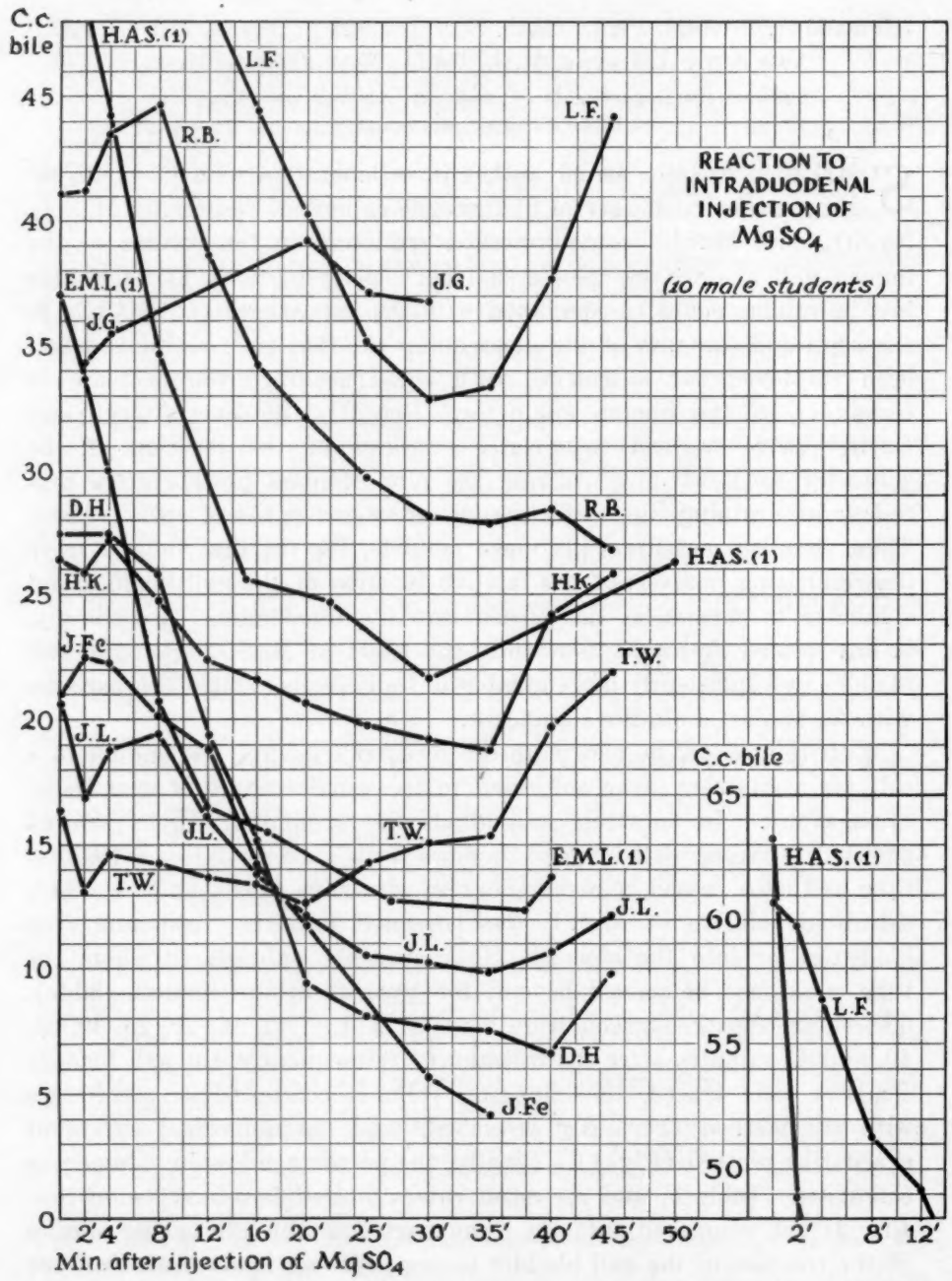

Fig. 1.—Individual contraction curves showing the rate of emptying of the gall bladder in ten students receiving 30 c.c. of a saturated solution of $MgSO_4$ intraduodenally (cf. Tables I and IIIA). Ordinates, volume of gall bladder as calculated from cholecystograms (for method see Boyden).[3] Abscissas, minutes after injection of salts into duodenum.

TABLE I

REACTION OF HUMAN GALL BLADDER TO INTRADUODENAL INJECTION OF $MgSO_4$

10 MALE STUDENTS	AGE	WT.	"B"* BILE MIN.	VOLUME OF GALL BLADDER AT INTERVALS AFTER $MgSO_4$											
				2 MIN.	8 MIN.		12 MIN.		20 MIN.		30 MIN.		40 MIN.		
				C.C.	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	C.C.	PER CENT LOSS	
R. B.	23	170	16	41.18(0)	(44.62)	00.00	38.67	6.10	32.13	21.98	28.20	31.52	(28.48)	31.52	
J. Fe.	21	170	8	20.66(0)	20.22	2.13	18.89	8.57	11.81	42.84	5.76	72.12	4.13(35′)	80.00	
L. F.	21	165		59.63	51.07	14.36	49.15	17.58	40.29	32.44	32.91	44.81	(37.64)	44.81	
J. G.	20	165		34.4	(35.37) (4′)	0.00	–	0.00	(39.26)	0.00	(36.8)	0.00	–	0.00	
D. H.	23	175	18	27.4(0)	25.93	5.37	19.29	29.60	9.40	65.69	7.65	72.08	6.59	75.95	
H. K.	23	165	18	25.93	24.85	4.17	22.38	13.70	20.71	20.13	19.26	25.73	18.79(35′)	27.54	
J. L.	23	155	12	18.86	(19.43)	0.00	16.14	4.81	12.05	29.00	10.33	39.13	9.89(35′)	41.72	
E. M. L. (1)	24	152	8	33.66	20.7	38.50	16.38	51.34	14.32	56.63	12.70	62.77	12.42	63.10	
H. A. S. (1)	21	155		63.18(0)	34.65	45.16	29.5	53.31	25.00	60.43	21.69	65.67	(23.95)	65.67	
T. W.	23	150		13.08	(14.33)	0.00	13.72)	0.00	12.30	5.96	(15.00)	5.96	(19.83)	5.96	
Total	221	1622	80			109.69		185.01		335.10		419.79	[illegible]	436.27	
Average	22	162	13.3			10.97		18.50		33.51		41.98		43.63	
5 yolks by mouth—12 male students (Boyden,[3] Boyden and Grantham[6])						14.26		27.96		43.51		55.67		64.55	
1 yolk by duod. tube—9 male students (Boyden and Berman[5])						17.87		34.28		57.62		70.99		–	

*First noted in aspirated duodenal contents.

it causes discharge of only 42 per cent whereas egg yolk induces evacuation of 71 per cent of the contents of the biliary vesicle in the first 30 minutes after the fluid reaches the duodenum (Fig. 2 and Table I).

A similar statement regarding the action of $MgSO_4$ upon the sphincter may be made by comparing the data of Bergh and Layne[2] with that of Bergh.[4] In these manometer studies of cholecystectomized patients with T tubes in the common duct it was observed that when $MgSO_4$ was injected into the duodenum (Table II*B*) the mean fall in resistance was only 3.1 cm. of water, whereas in fifteen patients receiving two egg yolks mixed with cream the fall averaged 7 cm. (Table II *C*).

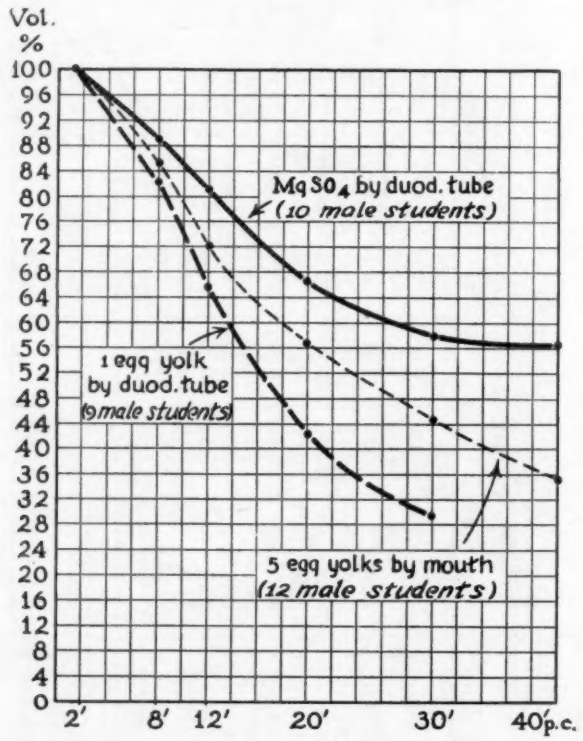

Fig. 2.—Mean curves comparing rate of emptying of the gall bladder in ten students receiving $MgSO_4$ intraduodenally with rate in students of comparable age receiving egg yolk orally (cf. Boyden and Grantham)[6] and intraduodenally (cf. Boyden and Berman).[5] Ordinates, volume of gall bladder; abscissas, minutes after salts or egg yolk.

Secondly, these data indicate that although the effectiveness of $MgSO_4$ is much less than that of egg yolk, it merely differs in degree, i.e. that it acts both upon the gall bladder and upon the sphincter for the same time and in the same way as egg yolk but with less force. Thus, under the stimulus of $MgSO_4$, emptying of the gall bladder first ceased 33.1 minutes after the drug had been administered (average for 9 students, Table III*A*) and with egg yolk, over 32 minutes afterward (average for 9 male students, Table III*B*)[1, 5]; with oral administration it took 32.5 minutes (average for 12 male students, Fig. 2).[3, 6] Similarly the maximum fall in sphincter resistance in the patients of Bergh and Layne occurred, respectively, at 21.4 and 21.7 minutes after $MgSO_4$ had been

TABLE II

EFFECT OF $MgSO_4$ UPON SPHINCTER OF ODDI*

PATIENT	FIRST RESPONSE (MIN.)	FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)		ORIG. LEVEL RECOVERED (MIN. AFTER DRUG)
			IN CM.	MIN. AFTER DRUG	
A. Changes in resistance following oral administration of drug					
1	0-up	6	3	47	54
2	0-up	4	8	26	60+
3	6-up	13	Remains above original level		
4	2-down	2	6	12	31
5	3-up	6	3	28	41
6	0-up	6	3	17	35
7	0-up	3	3	5	60
8	12-down	12	3	22	26
9	6-down	6	6	24	32
10	6-down	6	5	18	60+
11	4-down	4	1	6	7
12	4-down	4	5	30	49
Mean	12)43	12)72	11)46	11)235	11)455
	3.6	6	4.2	21.4	41.4
B. Changes in resistance following injection into duodenum					
1†	1-up	5	5	9	52
2	0-up	4	Returns to original level		
3	0-up	5	2	33	53
4	0-up	2	2	37	60+
5	0-up	6	2	14	24
6	4-up	8	1	10	12
7	0-up	10	6	18	34
8	0-up	4	4	26	45
9	0-up	2	Returns to original level		
10	0-up	3	Remains at high level		
11	0-up	2	1	12	24
12	0-up	4	5	36	48
Mean	12)5	12)55	9)28	9)195	9)352
	0.4	4.6	3.1	21.7	39.1
C. 14 patients given 2 egg yolks and cream by mouth‡					
Mean	-	4	7	21	38

*Analysis of data in article by Bergh and Layne[2] for comparison with gall bladder studies.

†These are not the same patients that are listed in *A*.

‡Bergh.[4]

administered (average for 11 and 9 patients, Table II*A* and *B*) and with egg yolk, 21 minutes afterward (average for 14 patients, Table II*C*). Indeed, even the period of return to the original level of resistance was approximately the same—41.4 and 39.1 minutes for $MgSO_4$ (Table II*A* and *B*) and 38 minutes for egg yolk (Table II*C*).

These parallel studies also permit a third major conclusion: namely, that while egg yolk and $MgSO_4$ act for the same period and in the same way upon the gall bladder or upon the sphincter, and differ only in the degree of their effect, the end organs react differently to either stimulus. Thus, while emptying of the gall bladder continues until an average period of 31 to 33 minutes has elapsed after $MgSO_4$ or egg-yolk has been administered, lowering of the sphincter resistance ceases after an average of 21 to 22 minutes; the figures for the actual duration of fall in volume

TABLE III

ANALYSIS OF CONTRACTION CURVES OF GALL BLADDER

PATIENT	FIRST RESPONSE (MIN.)*	FIRST FALL BEGINS (MIN.)	MAIN FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)	
				MIN. AFTER INJECTION†	DURATION OF MAIN FALL
A. Changes in volume following injection of 30 c.c. of $MgSO_4$ into duodenum in 10 male students					
R. B.	0-up	8	8	35	27
J. Fe.	0-up	2	2	35	33
L. F.	0-down	0	0	30	30
J. G.	0-up	(20)	(20)	--	--
D. H.	0-up	4	4	40	36
H. K.	0-down for 2′	0	4	35	31
J. L.	0-down for 2′	0	8	35	27
E. M. L.	0-down	0	0	38	38
H. A. S.	0-down	0	0	30	30
T. W.	0-down for 2′	0	4	20	16
	0	9)14	9)30	9)298	9)268
Mean		1.5	3.33	33.1	29.8
B. Changes in volume following injection of 1 egg yolk into duodenum in 9 male students‡					
W. F.	0-down	0	0	35+	35+
M. K. (1)	0-down for 2′	0	4	33+	29+
G. A. K.	0-down	0	0	25	25
E. D. P.	0-down	0	0	40+	40+
A. R.	0-up	2	2	30+	28+
M. M. S.	0-down	0	4	30+	26+
T. J. W.	0-down	0	0	32	32
A. D. W. (1)	0-down	0	0	27	27
A. D. W. (2)	0-down for 4′	0	9	38+	29+
	0	9)2	9)19	9)290	9)271
Mean		0.2	2.1	32.2+	30.1+

and of duration of resistance are approximately 30 and 17 (cf. column 6, Table III*A* and *B*, and the figure obtained by subtracting column 3 from 5 in Table II*B* and *C*). Similarly, the initial response of the end organs to either agent is different. Thus, while the gall bladder in the majority of patients first reacts to one or the other stimulant by contraction (19 out of 24 individuals ingesting egg yolk, Table III*C* and *D*; 8 out of 9 taking egg yolk by tube, Table III*B*; and 6 out of 10 individuals injected with $MgSO_4$, Table III*A*), the sphincters first react in more than one-half of the patients by increased resistance (7 out of 14 patients ingesting egg yolk, Bergh,[4] 6 out of 12 taking $MgSO_4$ by mouth, Table II*A*; and 12 out of 12 taking it by duodenal tube, Table II*B*).

Finally, it may be noted that duodenal administration of $MgSO_4$ is no more effective in its action upon the sphincter than oral administration. The fall in resistance begins sooner with the duodenal injection (4.6 minutes, Table II*B*) than after ingestion of the drug (6 minutes, Table II*A*) and ends sooner, but the total fall is slightly less (3.1 as against 4.2 cm.). No comparison is available for egg yolk.

In respect to the gall bladder reaction, only four individuals have been tested orally with $MgSO_4$. Two of them averaged a discharge of

TABLE III—CONT'D

PATIENT	FIRST RESPONSE (MIN.)*	FIRST FALL BEGINS (MIN.)	MAIN FALL BEGINS (MIN.)	MAXIMUM FALL (BELOW ORIGINAL LEVEL)	
				MIN. AFTER INJECTION†	DURATION OF MAIN FALL
C. Changes in volume following oral administration of egg yolk to 12 male students§					
L. J. B.	0-down	0	0	20	20
K. L.	0-down for 2′	0	4	25	21
I. D.	0-up	2	2	35	33
F. K. H.	0-down for 2′	0	4	20	16
N. A. C.	0-down for 2′	0	8	35	27
L. O. M.	0-down for 2′	0	4	45+	41+
J. S. L.	0-up	4	4	40+	36+
W. A. G.	0-down for 4′	0	12	45	33
R. C. C.	0-up	8	8	35	27
R. L. W.	0-down	0	0	20	20
R. J. B.	0-up	2	2	30	28
N. B. B.	0-down for 2′	0	4	40	36
	0	12)16	12)52	12)390	12)338
Mean		1.3	4.3	32.5	28.2
D. Changes in volume following oral administration of egg yolk to 12 female students§					
R. S.	0-down	0	0	20	20
F. E. D.	0 down for 4′	0	8	45+	37+
E. E.	0-down for 4′	0	8	30	22
C. L. B.	0-down for 2′	0	4	30	26
H. H. K.	0-down for 2′	0	4	25	21
K. L. L.	0-down for 2′	0	4	45+	41+
L. R. F.	0-down for 2′	0	4	25	21
A. H. H.	0-down	0	0	25	25
H. H. S.	0-up	8	8	45+	37+
S. M. O.	0-down	0	0	35	35
J. M. L.	0-down for 2′	0	4	30	26
C. H. S.	0-down	0	0	16	16
		12)8	12)44	12)371	12)327
Mean		0.7	3.7	31	27.25

*Sometime between 0 and 2 minutes Pc. (Earlier studies, Boyden,[3] suggest the latent period is about 1 minute.)

†At this time filling begins.

‡From data of Boyden and Birch,[1] (Table I) as summarized by Boyden and Berman,[5] (Table III).

§After data in Boyden and Grantham,[6] Fig. 2.

45 per cent in 40 minutes but the other two showed little, if any, response to the drug. In the absence of a sufficient number of cases it can be stated merely that $MgSO_4$ when administered orally may induce as marked emptying of the gall bladder as when given by duodenal tube. The studies on egg yolk are conclusive. When this food is given by duodenal tube it causes not only a more pronounced emptying (71 as against 55.7 per cent in the first 30 minutes, Table I; Fig. 2), but the initial response is quicker—the main phase of emptying beginning at an average of 2.1 minutes after duodenal administration (Table III*B*), as compared with 4.3 minutes after oral administration (Table III*C*).

Incidentally Table III*C* and *D* emphasizes the nature of the sex differences previously reported.[3, 6, 7] The data show that the time intervals are comparable, the main fall in volume for male students beginning at 4.3 minutes pc. and having a duration of 28.2 minutes, the cor-

responding figures for female students being, respectively, 3.7 minutes pc. and 27.25 minutes. Since, however, males of this age discharge approximately two-thirds of the contents of the gall bladder in the first 40 minutes after a meal of egg yolk and females nearly three-fourths (cf. Table III, Boyden and Fuller),[7] it would seem either that the gall bladder contracts with greater force in the female or that the drop in sphincter resistance, in this sex, is greater. It would be desirable, therefore, to ascertain whether or not there are sex differences in the reaction of the sphincter to egg yolk.

DISCUSSION

The striking fact that $MgSO_4$ acts for the same length of time as egg yolk and merely differs in the degree to which it affects the gall bladder or the sphincter strongly suggests that its mechanism is not local, as hitherto supposed, but hormonal and that it is absorbed by the intestinal epithelium and causes the formation of a cholecystokinin-like substance which stimulates the gall bladder to contract and the sphincter to relax. The fact that it does not cause as deep contraction or as great relaxation as egg yolk may be explained on the basis that magnesium is not absorbed as readily, or that it is not chemically so effective.* In order to prove a hormonal mechanism it would be necessary to find an animal in which the biliary tract responds to magnesium sulfate† and to resort to such cross-circulation experiments as Ivy and Oldberg employed.[10] Nevertheless, it is believed that the circumstantial evidence presented above strongly favors the existence of such a mechanism.

The second striking fact—the differing reaction of the gall bladder and sphincter to a given stimulus ($MgSO_4$ or egg yolk)—suggests the intrusion of a second factor. What is it that modifies the response of the sphincter, but not that of the gall bladder, to what is presumably an intestinal hormone? Reasoning from the data provided by animal and human experimentation, it may be assumed that the sphincter is under tonic contraction, except after meals, and therefore any force that releases it must overcome greater resistance than it would in the case of the gall bladder. Accordingly, if a given stimulus (e.g., a hormone in the blood) were applied at the same time to both the gall bladder and sphincter, its effect upon the sphincter might be expected to be delayed and, in the end, more quickly dissipated. In support of this it may be stated that sectioning of nerves to the biliary tract in cats leaves one with the inference that the sphincter is kept contracted by its own intrinsic nerve net rather than by extrinsic nerves, for when all nerves to the choledochoduodenal junction are severed the only effect is a marked retardation in the evacuation of the biliary tract after ingestion

*According to Hirschfelder,[8] 20-30 Gm. $MgSO_4$, 7 H_2O by mouth does not significantly raise the blood magnesium, and about 40 per cent is excreted in the urine in 24 hours.

†Recently Kozoll and Necheles[9] have shown that magnesium and sodium sulfate have variable effects upon the sphincter of dogs and no effect on the gall bladder of that species. Similarly Boyden and Birch[1] were unable to induce contraction of the gall bladder in cats by injection of $MgSO_4$ into the duodenum.

of egg yolk; i.e. the only extrinsic motor nerves that are eliminated by the experiment are the inhibitors of sphincter contraction (Johnson and Boyden[11]).

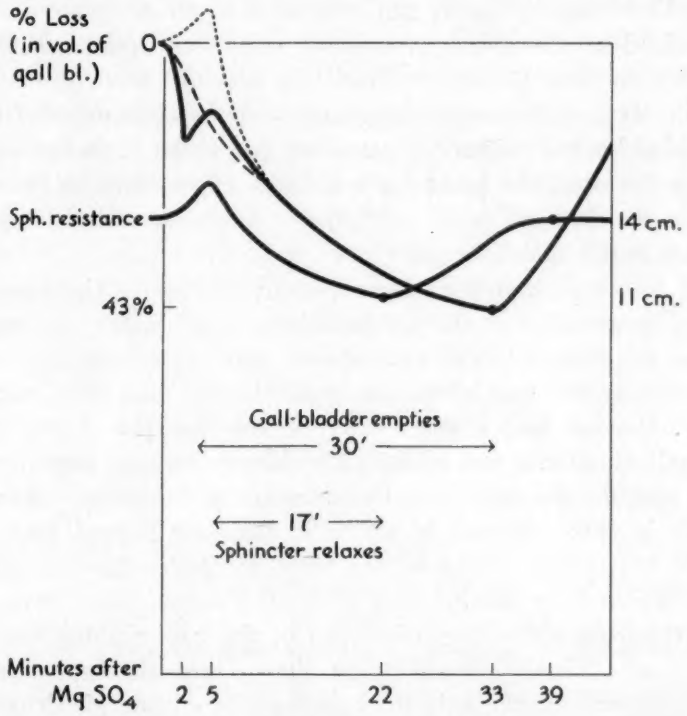

Fig. 3.—Graph illustrating sequence of events after duodenal administration of $MgSO_4$. Upper lines, curves recording average decrease of 43 per cent in volume of 10 gall bladders (cf. Table III*A*). Dotted line, 3 cases (R. B., D. H., and J. Fe., Fig. 1) in which the gall bladder first reacted by relaxing, thereby appearing to increase its volume temporarily; dash line, 3 cases (H. A. S., L. F., and E. M. L.) in which the gall bladder reacted by contracting only; solid line, 3 cases (H. K., J. L., and T. W.) in which it first contracted (for 2 minutes), then relaxed (for an average of 3 minutes), then entered its main phase of contraction. Lower solid line, curve recording mean changes in resistance of sphincter in 12 patients (cf. Table II*B*). In all 12, the sphincter reacted first by increasing its resistance (from an average manometer reading of 14. to 15.5 cm. of water), then its resistance fell gradually to 11 cm., then rose to 14. Note that the gall bladder empties for an average period of 30 minutes, while the sphincter relaxes for an average period of only 17 minutes.

Accepting these two hypotheses as starting points one may reconstruct the usual sequence of events as follows (Fig. 3). Within a minute or so after an effective substance enters the duodenum the gall bladder begins to contract under the stimulus of the circulating hormone. The sphincter, however, first reacts by increasing its resistance to the passage of bile, more so in the presence of $MgSO_4$ than egg yolk. Quite likely this is the effect of local irritation upon a muscle already under sustained tonus. This rising resistance is maintained, on the average, for about 4½ minutes (Table II*B*). If the period is shorter, probably the gall bladder continues to empty (dash line, Fig. 3); if longer, or more intense, the gall bladder probably relaxes (solid line, Fig. 3), usually for 2 or 3 minutes, the so-called "two-minute pause."[3] It is suggested that this sudden relaxation is the reaction of a local nerve net in the gall bladder wall to a suddenly increased load and that it is comparable

to what happens when bile backs up into the gall bladder during fasting; namely, the gall bladder adjusts itself to the increased pressure in the biliary tract.* Soon, however, the accumulating hormone prevails over the sphincter and the latter's resistance decreases for an average period of about 17 minutes (Fig. 3), until the level of the hormone drops below the threshold of the sphincter's nerve net; then resistance slowly increases for another 17 minutes until the original level of resistance is regained. Meanwhile, under the stimulus of the accumulating hormone, the gall bladder has resumed contraction and keeps it up for an average of 30 minutes until the sphincter resistance approaches its fasting level. This ends the first phase of emptying. A new spurt of food sets the mechanism going again.

It will be noted that the above account eliminates the necessity for reciprocal innervation of the gall bladder and sphincter. In support of this view, Bergh and Layne have shown that the human sphincter goes through its cycle even when the gall bladder has been removed.[2, 4] Secondly, Boyden and Rigler[12] have shown that the emptying of the human gall bladder is not inhibited by severe faradic excitation of the stomach and duodenum. Thirdly, Johnson and Boyden[11] have shown that even in cats—animals in which it has been proved that the vagi accelerate evacuation of the biliary tract by increasing the tone of the gall bladder and by diminishing that of the sphincter—even in such animals egg yolk still causes emptying of the gall bladder after section of both vagi. Finally, Bergh[14] has shown that the human sphincter does not respond significantly to cholinergic or adrenergic drugs.

The existing evidence, therefore, favors the view that in man the gall bladder and the sphincter react independently to a given hormone in the blood stream, the one by contracting, the other by relaxing; and that the tone of the sphincter is maintained by its local nerve net. Perhaps this explains why it has not been possible as yet to relieve spasms of the sphincter unless antispasmodic drugs are employed—substances like amyl nitrite and nitroglycerin which act directly on smooth muscle—or such hormone-producing substances as $MgSO_4$ and egg yolk.

SUMMARY

1. Magnesium sulfate is an effective agent in evacuating the human biliary tract, but is inferior in this respect to egg yolk. Thirty cubic centimeters of a saturated solution introduced directly into the duodenum induces, within 30 minutes, an average decrease of 42 per cent in the volume of the gall bladder and lowers the sphincter resistance 3 cm. of water (manometer reading). In the same interval egg yolk lowers the gall bladder volume 71 per cent and the sphincter resistance 7 cm.

*One reason why it is not considered to be a reflex inhibition of the gall bladder is that reflexes from the stomach and duodenum to the gall bladder cannot be demonstrated in man (Boyden and Rigler)[12] as in animals (Birch and Boyden).[13]

2. Magnesium sulfate acts upon gall bladder and upon sphincter in the same way and for the same length of time as egg yolk. It differs only in degree, a characteristic which may be attributed to slower absorption rate or less effective chemical action. Accordingly, it is suggested that magnesium sulfate, like egg yolk, is to be considered as a hormone-producing substance which acts independently, through the blood stream, upon both the gall bladder and the sphincter of Oddi.

3. The two end organs, however, react differently to a given stimulus. Initially, a dose of either egg yolk or magnesium sulfate usually causes the sphincter to contract. This, in turn, may interrupt the contraction of the gall bladder which is just getting under way, thereby producing the so-called "two-minute pause." By the end of the first 4 or 5 minutes, however, the sphincter enters a period of progressive relaxation which lasts for an average period of 17 minutes. Meanwhile, the gall bladder begins its main phase of contraction which lasts for an average period of 30 minutes. Evidence from animal experimentation suggests that the reason why the hormone acts upon the sphincter for a shorter time than upon the gall bladder is that during fasting the tone of the sphincter is maintained by a local nerve net which has a higher threshold than that of the gall bladder.

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PERFORATIONS OF THE GALL BLADDER OCCURRING IN A GENERAL SURGICAL PRACTICE IN A MODERATE-SIZED COMMUNITY

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NIEMEIER[1] in an article on the subject of perforations of the gall bladder separated the varieties of perforation as follows: (1) Perforation with communication with another viscus; (2) perforation with formation of a pericholecystic abscess, and (3) acute free perforation. Of the latter he cites one case with recovery. To these should be added external rupture of the gall bladder because of a case reported by Doran[2] in which an empyema of the gall bladder ruptured externally and established a fistula through which stones passed. X-ray visualization demonstrated an external biliary fistula.

Of the first type in Niemeier's classification, Jaffe[3] reported a case with rupture into the duodenum, followed by obstruction of the intestine by a large gall stone. In another case[3] two communications were present, one into the transverse colon and the other into the duodenum. In another case[3] the perforation was found to be into the liver. In two of our cases there were perforations into the liver and since there appeared to be considerable difference clinically between these cases and those which perforate into another organ, they should probably be classified separately. Therefore, to recapitulate, perforations of the gall bladder should be classified under five general types:

(1) Perforation with communication with another viscus; (2) perforation with formation of a pericholecystic abscess; (3) acute free perforation; (4) perforation into the liver; (5) external perforation.

The etiology of gall bladder perforations is essentially that of cholecystitis and cholelithiasis, plus some other factor, or factors, which are not established. There was no correlation in our cases between any predisposing or bodily factors and perforation, unless it was the age of the patient. With one exception, all were over 56 years of age. The incidence in our practice seems relatively high, namely, six cases in five years. Three other surgeons in this community have seen, respectively, two, one, and two cases in many more years. One of them also saw a case of perforation caused by an ice pick which had been thrown at the patient. The incidence in the New York Hospital as stated by Hotz[4] was 115 perforations out of 3,880 operations on the gall bladder,

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or 3 per cent. At the Mayo Clinic, Judd and Phillips[5] reported sixty-one cases in ten years. Eliason and McLaughlin[6] stated that the general incidence was found to be approximately from 1 to 3 per cent of all cases of biliary diseases.

Many facts are known regarding the pathogenesis of gall bladder disease, since it is fairly common and has been recognized for many years. It is doubtful that perforation of a normal gall bladder ever occurs, except from outside trauma. And, of the diseased gall bladders, many are found sterile upon culture, so it is probable that infection is secondary. Graham and Peterman[7] seem to have established the origin of the infection factor as lymphatic extension from neighboring viscera. The original damage is probably brought about by a combination of several factors, which can be summarized in the following paragraphs.

Cole, Novak, and Hughes[8] demonstrated in dogs that chronic partial obstruction of the gall bladder would cause inflammatory changes, but not necessarily bacterial inflammation. They produced surgically a flap of mucosa at the junction of the cystic duct with the gall bladder, the result of which was a "strawberry gall bladder" after varying lengths of time. Womack and Bricker[9] reported a method of experimental production of acute cholecystitis. They withdrew normal bile from normal dogs' gall bladders, concentrated it 50 per cent by evaporation, and reinjected it into the gall bladder after first tying off the cystic duct. Varying degrees of acute inflammation were found at autopsy. Cultures from some of the more acutely inflamed organs were often found to be sterile. Controls, using normal saline solution to reinject into the gall bladder, were in every case negative, since the gall bladders remained unaffected. Therefore, in their experimental animals, acute cholecystitis resulted from an occlusion of the cystic duct with concentration of the occluded bile. Hellwig,[10] however, feels that it is very possible that, during the manipulations inherent in the experiment, reflux of pancreatic juice may have occurred. The admixture of trypsin with bile thus resulting may have been responsible for the changes that occurred, somewhat in the manner of the production of acute pancreatitis.

Glenn and Moore[11] recently reported twenty-five cases of perforation of the gall bladder. In their cases rupture into the liver was most common. They found in every case evidence of formation of Rokitansky-Aschoff sinuses and ascribed rupture to the formation of these sinuses. These structures are small outpouchings of the gall bladder mucosa into the muscularis, caused by increased intracystic pressure and weakening of the wall by inflammation. Jaffe[3] definitely ascribed rupture in one case to decubitus ulceration by a stone causing pressure necrosis in the neck of the gall bladder.

In the six cases here presented the constant symptom was pain in the gall bladder region, usually very severe, but not diagnostic of perforation. There was usually nausea and vomiting, and sometimes jaundice. The onset was usually acute, but not necessarily cataclysmic.

Meeker[12] operated upon a patient, for example, in 1939, who had gangrene with acute free perforation and symptoms simulating acute appendicitis. In each of our cases there was a history of indigestion, dyspepsia, or gall bladder colic. Tenderness over the gall bladder was the only constant finding. Rigidity was present when the perforation was free, and in the case in which a pericholecystic abscess had formed, there was a palpable mass as well as rigidity. Rigidity was not present when perforation had occurred into the liver. The temperature was below normal at first in the acute free perforated cases, but later was elevated, and was elevated in the other types of cases. The laboratory findings were of little value, and the x-ray of negative value only, ruling out intestinal obstruction and perforation of the stomach in two cases.

D'Abreou[13] reported three cases in which perforation had occurred in a series of 116 gall bladder operations. One of his conclusions was that the preoperative diagnosis was seldom made. One of the perforations occurred in a patient who was in bed on a starvation diet for treatment of acute cholecystitis, but in this case the diagnosis was made before operation. One of our cases occurred under very similar circumstances, but was thought to be a case of a perforated peptic ulcer.

After having observed three cases within six months, we were naturally very aware of the possibility of perforation of the gall bladder and soon had made two incorrect diagnoses. One, in which a mass in the right upper quadrant was present, with rigidity, tenderness, and jaundice, at operation proved to be a large tubal pregnancy which was adherent to the gall bladder. The free end of the right fallopian tube was deeply bile-stained. The other case occurred in a middle-aged man who had had a very acute onset of pain in the right upper quadrant, with nausea, vomiting, and rigidity. Although the diagnosis of perforation of the gall bladder was wrong, a gangrenous gall bladder was removed at operation with gratifying results.

The treatment of suspected perforation of the gall bladder without exception should be immediate operation. Therefore, it follows that many cases of acute cholecystitis will be operated upon because of a mistaken diagnosis of perforation. But, according to Hotz[4] and many others, immediate cholecystectomy for cases of acute cholecystitis is the procedure of choice. He feels, after reviewing 3,880 cases, that watchful waiting is not a safe procedure in acute cholecystitis. He states that perforation is a frequent occurrence, and that it is impossible to predict whether or not an acutely inflamed gall bladder will perforate. Furthermore, in his experience, localization with abscess formation has not been the rule in cases under conservative management. At the Mayo Clinic,[5] in sixty-one cases of perforated cholecystitis in ten years, there were six deaths, one-half of the deaths being associated with pulmonary complications. Cholecystectomy was done in forty-eight cases and cholecystostomy in thirteen.

Our series of cases is too small to warrant making any definite conclusions; nevertheless, it is fairly representative of the cases encountered in the average surgical practice in a moderate-sized community. We do feel that this study has indicated the surgical policy of early operation in all cases of fulminating acute cholecystitis rather than that of delayed or expectant treatment. In contrast to the problem of acute appendicitis, the physician usually observes acute cholecystitis early in the disease, and hence has the opportunity of influencing the exact mode of treatment from the first. Early observation of the patient is probably more frequent in private practice than in the larger clinics, as evidenced by a comparative study of reports appearing in the literature. Of our six cases, only two patients survived, one being operated upon early, the other rather late.

CASE 1.—A woman, aged 60 years, was admitted Aug. 28, 1940, complaining of pain in the right upper quadrant and jaundice, both of which had been present one month, very severe at first, but much less so in the week prior to entrance. There was a history of several attacks of colic previously and the patient had suffered from dyspepsia for many years. On examination the temperature was 100.4° F., pulse rate 100, and blood pressure 150/70. She was very obese and markedly jaundiced. There was mild tenderness over the gall bladder, but no rigidity or mass. The laboratory reported acholic stools, no bile in the urine, W.B.C. 22,650 with 70 per cent polymorphonuclears, Hb. 55 per cent, Kolmer negative, and icteric index 21. X-ray of the gall bladder was reported as nonvisualization of the gall bladder with a very large liver. The patient was treated medically until September 5 with dextrose, proteins, vitamin K, and sulfathiazole. On September 5 she was explored, eleven days after admittance, or about five weeks from the onset of her condition. At operation, marked biliary cirrhosis was noted. The gall bladder had perforated into the liver and formed a large abscess cavity containing thick pus and numerous small stones. The common and hepatic ducts were greatly dilated and contained pus and stones. The gall bladder was removed, a T tube placed in the common duct, and drains inserted into the cavity in the liver. The pathologist reported a necrotic gall bladder with stones and chronic cholecystitis. The patient's course was fairly good until October 1. On September 24, x-ray visualization of the duct system had been negative for obstruction. On October 1, she developed right-sided pleural effusion of bile-stained fluid, with atelectasis of the lung. The fluid was clear and sterile. Following repeated tappings, she slowly became worse, with a septic temperature, and died November 13. Post mortem showed both lungs to be atelectatic, with bilateral hydrothorax. The liver contained multiple small abscesses and was the seat of marked purulent cholangeitis.

This case represents type 4. There was no rigidity, which led the medical men who first saw her to conclude that surgery was not indicated at that time. Had the surgeons seen her first, we may not have recommended surgery either. The preoperative diagnosis was finally thought to be a ball-valve stone with Charcot's intermittent hepatic fever.

CASE 2.—A woman, aged 63 years, was admitted July 27, 1938. Her complaints upon entrance were severe pain in the region of the gall bladder for several hours. In the history there was dyspepsia, jaundice, and colicky attacks over the past several years. On examination, the temperature was 100° F., the pulse 72. She was very obese and not jaundiced. There was moderate tenderness over the gall bladder,

but no rigidity. The urine was negative, W.B.C. was 13,600, and Hb. 87 per cent. X-ray reported nonvisualization of the gall bladder. For six days she was treated conservatively and on August 1, was operated upon. At operation there was found empyema of the gall bladder, with many small stones, rupture into the liver with formation of an abscess cavity containing stones, and many adhesions. Fundusectomy was done, drains placed, and the ducts left unexplored. She had a very stormy course, running a septic temperature until death occurred August 13, on the twelfth postoperative day. Post mortem showed a generalized peritonitis with a small liver abscess and purulent cholangeitis.

Comment.—This was another case of perforation into the liver. It would seem better to operate in the first twenty-four hours after the onset of acute gall bladder symptoms where there is fever and increased leucocyte count, for delay is often fatal, enough so as to overshadow the mortality of early operation.

CASE 3.—A women, aged 60 years, was admitted Dec. 1, 1940, complaining of severe pain in the region of the gall bladder, not relieved by morphine, and present for one day. For fifteen years she had had dyspepsia and bloating, and for six years colicky attacks, with a great deal of interim gastric symptoms. She had never been jaundiced, however. On examination her temperature was found to be 97° F., pulse 100, and respirations 35. Tenderness and rebound tenderness were marked throughout the abdomen, more in the gall bladder area. There was generalized rigidity. The urine was negative, the W.B.C. 4,770 with 78 per cent polymorphonuclears, and Hb. 91 per cent. The Wassermann was reported as negative. A scout film of the abdomen showed no stones, no distended loops of bowel, and no air over the liver. At operation, two hours after admittance and twenty-four hours after the onset of the pain, free bile was found covering all the peritoneal surfaces and in considerable quantity. The gall bladder was full of stones, and the proximal third was gangrenous, with a large free perforation near the neck. Cholecystectomy was done and the abdomen closed with drainage. The course was uneventful and she was dismissed after twenty days. The pathologist reported chronic cholecystitis with stones.

Because of the acuteness of the symptoms, rather than the fact that the patient presented a "gall bladder" picture, she would have been operated upon by any surgeon who might have seen her. It is such cases that impress us with the desirability of early operation upon the acute gall bladder.

CASE 4.—A man, aged 78 years, was admitted Aug. 21, 1941. He had an acute onset of very severe pain in the abdomen, followed by nausea and vomiting. The pain was so severe he was unable to move. During eight hours he was watched, with the possibility of coronary thrombosis in mind. His temperature was 96° F., pulse 100, and blood pressure 180/100. There was no jaundice. Boardlike rigidity was present throughout the abdomen, with marked tenderness and rebound tenderness. The W.B.C. was 12,800, with 66 per cent polymorphonuclears, and Hb. of 16.9 Gm. A flat plate of the abdomen was negative. The patient had had two similar attacks of lesser severity in the last five years. At operation, about ten hours after onset, there was found free bile in the abdomen, a few adhesions about the gall bladder, and gangrene with perforation of the gall bladder. The gall bladder was contracted and contained several small stones. Partial cholecystectomy was done, leaving a drain in the neck. The pathologist reported acute cholecystitis with cholelithiasis. The patient immediately ran a very high temperature, which increased for four days, during which time he was irrational. He died on the fourth

postoperative day. At post mortem the heart, lungs, and kidneys showed nothing to account for death, and the liver was about normal.

The above patient was operated upon even earlier than the one previously cited, but died. The course was very suggestive of the "liver death" of Heyd.

CASE 5.—A man, aged 56 years, was admitted Feb. 26, 1942, complaining of cramps in the abdomen and gas on the stomach. There was a past history of indigestion, pain in the upper abdomen, nausea and vomiting for some years, and a gastroenterostomy two years previously. On examination, nothing much was found but the scar from his operation. The urine was negative, W.B.C. 6,600, Hb. 75 per cent, and Wassermann negative. Stomach x-rays were negative, other than confirming the gastroenterostomy. The gall bladder was not visualized with the dye. He was put on a modified Sippy regime until March 4, when he began having pain in the gall bladder region, nausea and vomiting. For four days he ran a temperature between 100 and 101° F., with a white blood count averaging 10,000. He improved until March 21, when operation was performed because of a sudden accession of pain and tenderness. At operation there was found free bile and free stones in the peritoneal cavity. There were many adhesions about the gall bladder, but the perforation was not found. A cholecystectomy was done and a large quantity of bile was drained. Progress was fairly good until the sixteenth postoperative day, when he signed a release and went home, still with some bile drainage from the wound.

This case is similar to the one cited by D'Abreou[13] and is unusual in that the treatment he was on is also that recommended for gall bladder disease, that is, small frequent feedings to avoid overstimulating the emptying reflex, but at the same time causing repeated minimal stimuli in order to keep a constant flow of bile into the duodenum. He was also on bed rest and received sedatives and antispasmodics.

CASE 6.—A young man, aged 23 years, was admitted Jan. 21, 1942, complaining of severe pain in the abdomen, nausea and vomiting, and a mass in the right side of his abdomen. These had been present four weeks, following an acute onset. In the meantime, he noticed some relief from warm moist compresses. He said that for five years he had been under treatment for ulcers. On examination, he was very tender and rigid in the region of the gall bladder and a very hard fixed mass could be felt in the gall bladder area. The urine was negative, W.B.C. 13,700, with 60 per cent polymorphonuclears, Hb. 12.8 Gm., and a red count of 4,000,000. Chest x-ray and a scout plate of the abdomen were negative. On January 24, three days after admittance, he was operated upon. There was an inflammatory mass which included abdominal wall, duodenum and colon, and lower border of the liver. In the center of the mass was an almost destroyed gall bladder with a liver abscess communicating with it. There were no stones. The remnants of the gall bladder were surrounded by a thin layer of purulent material. With considerable difficulty, the whole mass was removed. The pathologist reported ulcerative cholecystitis and chronic hepatitis. The patient's course was uneventful until February 5, when he developed small bowel obstruction and an enterostomy was performed. His condition was improved until February 24, when he had massive hemorrhages from the mouth and bowels and died. At post mortem, fresh blood was observed in the cecum, duodenum, and stomach, but the sources of the hemorrhages could not be determined. There was a chronic, indurated duodenal ulcer, but with no evidence of recent hemorrhage and no evidence of perforation.

This apparently was a case of perforation of the gall bladder, with formation of a pericholecystic abscess. The factor of liver damage looms

large here, as it does in all cases of gall bladder disease, and liver damage may be said to be the deciding factor in the surgical mortality of gall bladder disease. We are impressed over and over again with the necessity of considering the liver first of all in our gall bladder surgery. We are often reminded, also, of the frequent occurrence of gall bladder disease accompanied by chronic peptic ulcer and appendicitis, as Moynihan pointed out years ago.

In presenting these six cases, we were partly motivated by the desire to hold up examples of surgical procrastination. All the patients should have been operated upon much earlier (except in Case 2), when liver damage was minimal.

The advantages of early operation in perforated gall bladder disease are just as applicable to acute cholecystitis before perforation occurs. These advantages are that minimal liver damage is present, the lymphatics are sealed by inflammatory edema and exudate, the peritoneum is in a state of acute vaccination reaction, adhesions are not established, the planes of dissection are easily found and separated, often because of marked pericystic edema, and, finally, in case perforation has not occurred, a surgical catastrophe has been prevented.

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AN EXPERIMENTAL STUDY OF METHODS FOR CLOSING THE DUODENAL STUMP AFTER GASTRIC RESECTION

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THE reported operative mortality for gastric resection varies from 5 to 26 per cent.[1] Leakage from the duodenal stump leading to peritonitis is the major cause of death, according to Moynihan and Perelman.[2] The importance of proper closure of the duodenal stump in the Polya-Reichel or Hofmeister-Finsterer types of Billroth II partial gastrectomies is appreciated by surgeons, but critical evaluations of the various methods now employed have been sparse.

The Kerr-Parker procedure for closing the duodenal stump is the one recommended by the most recent American texts of operative surgery.[3] In this method, the duodenum is crushed with a clamp and sectioned flush with the proximal side of the clamp. A continuous Cushing seromuscular suture is then inserted which inverts the edges when the clamp is withdrawn and the suture pulled taut. A second row of seromuscular sutures serves to reinforce the closure. Several special clamps such as the Clute modification of the Furniss clamp[4] have been recently introduced to facilitate the duodenal closure, but their use also necessitates some duodenal crushing.

The procedure popularized by Doyen[5] is the one found in the older texts of operative surgery.[6] The duodenum is crushed with a clamp which is replaced by a ligature, then sectioned proximal to the ligature, and the stump inverted with a purse-string suture. This method requires the mobilization of a large area of duodenum, a procedure frequently rendered difficult by the retroperitoneal attachments of the human duodenum, especially when the latter is the site of an ulcer.

Von Haberer recommends the open method in which no clamps are used. The duodenum is sectioned, the distal end closed with a continuous Connell suture, and a second row of continuous seromuscular sutures inserted.[7] Lahey prefers this method, but only because it does not waste as much duodenum as the Kerr-Parker closure. He states that if the edges are crushed first with a clamp, a better result is obtained.[8] Steinberg, on the other hand, believes that it is not advisable to use crushing clamps on the duodenal stump because clamps crush and devitalize tissue and thus jeopardize successful closure.[9] Both Lahey and Steinberg recommend fine chromic catgut for the first row of sutures, and the silk for the second row.

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Perelman, using ten dogs to study duodenal closure, concluded that the Kerr-Parker method gave the best results. He states that the more firmly the bowel is crushed, the better the stump will heal, and that the purse-string method gave the poorest stump. His opinion of the condition of the stump postoperatively was based solely upon gross and microscopic examination.

The object of this experiment was to perform gastric resections on a large series of dogs, evaluate the three fundamental types of duodenal closures by means of a quantitative method, and thus develop a "base" for comparison in future studies.

METHODS

Gastric resections were performed on ninety-six dogs. The duodenum was closed with chromic twenty-day 000 Armour's catgut in seventy-two animals, and with silk in the remaining twenty-four. The dogs were divided into four series of twenty-four each, according to the types of closure which were:

Series I. Von Haberer open method without clamps or crushing (catgut).

Series II. Crushing clamp method of Kerr-Parker (catgut).

Series III. Simple ligature followed by purse-string method without clamps or crushing (catgut).

Series IV. The same procedure as in Series III except that Size A black silk twist (Belding Corticelli) was substituted for catgut.

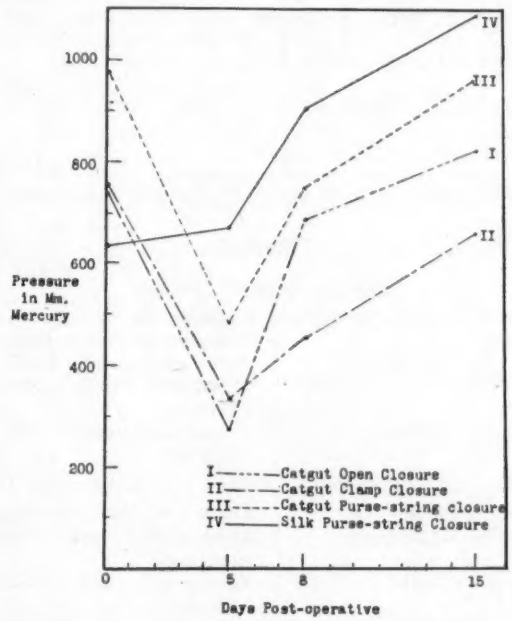
Horsley and others have emphasized that back pressure in the duodenum after Billroth II operations leads to separation and leakage.[10] For this reason we decided that the best method for measuring the strength of the duodenal closure would be to determine the air pressure necessary to blow out the stump. This was done by sectioning the duodenum at its distal untraumatized end, inserting a glass tube which was then tied in place, and connecting the tube to a bicycle pump through a specially constructed, large mercury manometer. The intraluminal pressure of the duodenum could thus be increased until rupture occurred, at which moment the pressure reading on the manometer was noted.

Each series of twenty-four dogs representing one type of closure was subdivided into four groups of six dogs each. In the first group of each series, the duodenal stump was blown out at the conclusion of the operation; in the second group this procedure was carried out on the fifth postoperative day, and in the third and fourth groups, on the eighth and fifteenth postoperative day respectively.

RESULTS

Table I shows the average pressures required to "blow out" the duodenal stump at the selected postoperative intervals. These figures have

been graphed in Fig. 1 to facilitate interpretation of results. The curves of all the catgut closures follow a similar pattern. The resistance to pressure falls to the lowest point on the fifth postoperative day, after which it rises steadily so that by the fifteenth postoperative day it is almost the same as immediately after the operation. The silk closures, however, show no postoperative drop but progressive increase in the resistance of the stump from the day of operation to the termination of the experimental observation period.



Statistical studies were made on all our data because the variations within a group may be as large as the difference between the means of any two groups. Significance was determined by using Fisher's formulas and tables as given in his book on statistical methods, pages 128 and 177.[11]

The results of this statistical analysis are shown in Table II. Study of our results show that:

1. The ligature and purse-string type of closure is the strongest, for only on the eighth postoperative day does any other procedure (open method) come close enough to eradicate any significant difference.

2. The open (Von Haberer) and clamp (Kerr-Parker) types of closures have the same strength immediately after the operation and on the fifth postoperative day. On the eighth postoperative day, the open method is significantly stronger than the clamp method, and on the fifteenth, slightly so.

3. The silk purse-string closure is much weaker than the catgut purse-string closure immediately after the operation, but slightly stronger at all subsequent times.

TABLE I

PRESSURES REQUIRED TO "BLOW OUT" DUODENAL STUMP

	GROUP 1. IMMEDIATE P.O. PRESSURE TEST	GROUP 2. FIFTH DAY P.O. PRESSURE TEST	GROUP 3. EIGHTH DAY P.O. PRESSURE TEST	GROUP 4. FIFTEENTH DAY P.O. PRESSURE TEST
Series I. Catgut Open Closure (Von Haberer)	740*	275	689	826
Series II. Catgut Clamp Closure (Kerr-Parker)	755	329	458	662
Series III. Catgut Purse-string Closure (Modified Doyen)	982	486	750	962
Series IV. Silk Purse-string Closure (Modified Doyen)	629	675	904	1091

*Each number represents mean of pressures for six dogs, expressed in mm. mercury.

TABLE II

SIGNIFICANCE OF CATGUT

Immediate—Between:	*Fifth Postoperative Day—Between:*
Open and clamp —No significance	Open and clamp —No significance
Open and Purse-string —Slight significance	Open and Purse-string —Significant
Clamp and purse-string —Significant	Clamp and purse-string —Significant
Eighth Postoperative Day—Between:	*Fifteenth Postoperative Day—Between:*
Open and clamp —Significant	Open and clamp —Slight significance
Open and Purse-string —No significance	Open and Purse-string —Significant
Clamp and purse-string —Significant	Clamp and purse-string —Significant

Between Silk and Catgut Purse-String Method:

Immediate —Significant
Fifth postoperative day —Slight significance
Eighth postoperative day —Slight significance
Fifteenth postoperative day —Slight significance

CONCLUSIONS

1. In the closures employing catgut as suture material, the ligature and purse-string method (without the use of clamps) is the procedure which gives the strongest closure of the duodenal stump. In the human being, however, anatomic and pathologic considerations may frequently render this procedure impractical, and a choice must be made between the other two methods.

2. The open method of Von Haberer is preferred to the clamp closure of Kerr-Parker because between the fifth and eighth postoperative day (the period of greatest postoperative mortality) the duodenal stump in the clamp method shows much less resistance to intraluminal pressure.

3. Silk ligature followed by the silk purse-string method was found stronger than catgut after the first postoperative day. The trend toward using silk in closure of the duodenum is supported by our results.

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THE TREATMENT OF FLEXION DEFORMITIES OF THE KNEE

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WITH our hospital facilities strained to the utmost because of hospitalization insurance and the present military emergency, it behooves us to rehabilitate as many patients incapacitated with chronic arthritis as possible, at least to the point where they are not bedridden. Our municipal and county hospitals have many beds filled with patients who cannot be removed because of flexion deformities of the knees, so their treatment becomes a social and economic, as well as a medical problem.

It may be well to review some of the facts regarding these cases, and to stress the importance of a conservative point of view in dealing with them. As orthopedic surgeons, our interest in the problem pertains largely to correction, but we also know that many flexion deformities of the disabling type can be prevented, with attention to rest and maintenance of the proper position of the joints during the inflammatory stage of arthritis. Swaim[1] and others have stressed that this is the crux of the problem of preventing arthritic deformities, which are always flexion deformities and develop while the patient is in bed. With the ever increasing cooperation between medical men and orthopedic surgeons in treating arthritis, we may all do our share in the prevention of severe flexion deformities.

Flexion deformities of the knees may result from a variety of conditions, including spastic paralysis, poliomyelitis, fractures and other injuries, and tuberculosis, but the vast majority of cases is due to chronic arthritis of the infectious, rheumatoid, or atrophic type.

Haggart[2] has classified flexion contractures of the knee as follows: (1) arthrogenic, the result of a disturbance in the joint itself, usually rheumatoid or atrophic arthritis; (2) neurogenic, in which there is fixation brought about by contracture of a muscle or muscle group as a result of abnormal innervation; (3) myogenic, which may be paralytic as the result of muscular imbalance after poliomyelitis, or myositic, resulting from inflammatory processes in the adjacent muscles, particularly the hamstring group; (4) congenital, usually associated with flexion contractures elsewhere in the body; and (5) static, consequent on hip flexion, short gastrocnemius, or faulty posture.

Although each case of flexion deformity must be considered as an individual problem, in which the patient's general condition, age, length of disability, and the degree of involvement of the various tissues of the

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joint are the most important factors, it always is necessary to proceed with a clear conception of the mechanical features of contracture, of the normal function of the knee joint, and of the relation of the anatomic structures which may block extension.

Both Silver[3] and Wilson[4] have stressed the role of the capsule, as well as the flexor muscles, in the deformity, and their operative procedures have been directed primarily to these structures. An outstanding feature of our own experience has been that many of the severe flexion deformities, particularly in atrophic arthritis, can be corrected at operation by releasing contracted structures other than the posterior joint capsule. When the marked contracture of the deep popliteal fascia is completely resolved, a major portion of the deformitiy is overcome. This experience coincides with that of Kulowski[5] who stated that among the many tenotomies performed at the University of Iowa Clinic, surprisingly few cases required additional capsuloplasty. He pointed out that "fortunately the capsule is the last structure to take part in the contracture and that posterior capsular shrinkage does not occur in myogenetic contractures unless a very long period has elapsed."

The structures of the knee joint are meagerly described in the standard works on anatomy, and hence we are indebted to Normand L. Hoerr,[6] professor of anatomy of Western Reserve University Medical School, for the following description. "The deep fascia of the popliteal region is a direct continuation of the fascia lata of the thigh, and over the popliteal fossa it is sometimes thin but always possesses considerable strength, owing to the numerous transverse fibers which are interwoven with longitudinal fibers. This deep fascia, which can be called popliteal fascia proper, is firmly attached on each side to the tendons of the muscles which bound the popliteal fossa; that is, the hamstrings above, and the plantaris and gastrocnemius below. The deep fascia is directly continuous with the connective tissue sheaths of the various muscles forming the boundaries of the popliteal fossa. The popliteal artery, popliteal vein, and sciatic nerve are held together by a sheath of fascia which is sometimes membranous, but often quite loose and containing considerable fat. Below the broad sheet of deep fascia which forms the roof of the popliteal space, the fascia becomes much looser and affords a fatty packing of the entire popliteal space. The floor of the popliteal fossa is formed from above downwards by (1) the popliteal surface of the femur, (2) the capsule of the knee joint, and (3) the strong fascia which covers the popliteus muscle. The resistant fascia roofing the popliteal fossa unites with the tendons and muscles, forming the walls of the space, and covers a well-delimited cavity, incapable of great distension." (Fig. 1.)

As Kulowski has explained, "the position of contracture is dependent upon the normal mechanics of the knee and follows definite physical laws. The key to the contracture complex is the flexion position. The associated elements are secondary phenomena directly dependent upon

it. The contracture position is therefore a fixed exaggeration of the normal flexion, incident to the newly established muscular equilibrium, and is certainly not a haphazard event.''

In any attempt at correction of a flexion deformity of the knee, the treatment must be planned to take into consideration the nature and extent of the underlying disease process and the tissues which are actually involved in the contracture; the mechanical devices used to aid in extension must be applied with attention to the physical laws which govern the function of the joint.

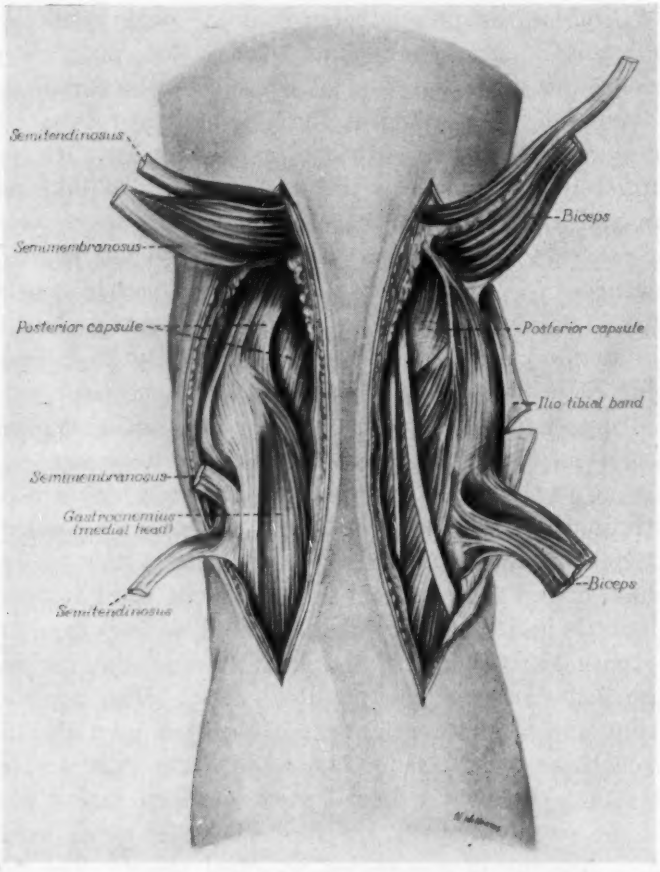

Fig. 1.—Posterior compartment of the knee joint with the deeper structures exposed, showing the popliteal fascia extending around the gastrocnemius muscle and between the muscle fibers.

The first consideration in the treatment of flexion deformities of the knee is a careful selection of cases. Surgical procedures are contraindicated in the presence of an inflammatory condition of the joints. The advice of an internist or someone particularly interested in the treatment of arthritis should be sought in all cases in which there is any question of continued activity of the disease process. When there is joint destruction so severe that ankylosis will certainly result or there

is no hope of restoring a functional joint, surgical treatment is useless. In polyarthritis, we have found to our dismay in one or two instances that the patient should not be subjected to surgery unless he is able to use his upper extremities well enough to aid himself in getting in and out of bed. Aged patients and those whose general condition make them poor operative risks also should not be subjected to a corrective procedure.

When patients have been properly selected with these factors in mind, it then becomes important to determine the extent of involvement of the joint structures, and consequently the type of treatment necessary. The procedure in most cases must be surgical release of the contracted tissues, followed by mechanical procedures to increase extension

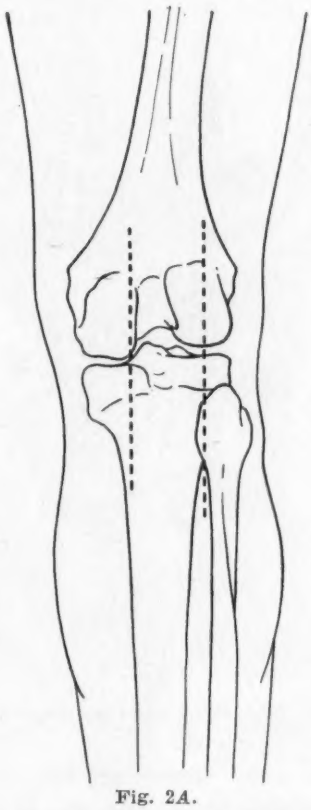

Fig. 2*A*.

Fig. 2, *A* and *B*.—Lateral and medial incisions of the knee.

of the joint. Closed methods, such as manual manipulation and the application of traction are satisfactory only in the mildest cases, but one should not hesitate to use them when they will suffice. In the majority of instances, the problem becomes one of deciding the extent of surgical correction which will be necessary.

It is difficult, if not impossible, to determine by diagnostic means whether the contracture is extra-articular or intra-articular. Kulowski

has stated that the block due to capsular shrinkage can be determined clinically by the presence of a posterior springy resistance against passive extension of the knee in the presence of relaxed hamstrings. In our own experience, this finding has limited application because when there is intracapsular involvement the extracapsular structures, particularly the hamstrings, are also contracted, as a rule.

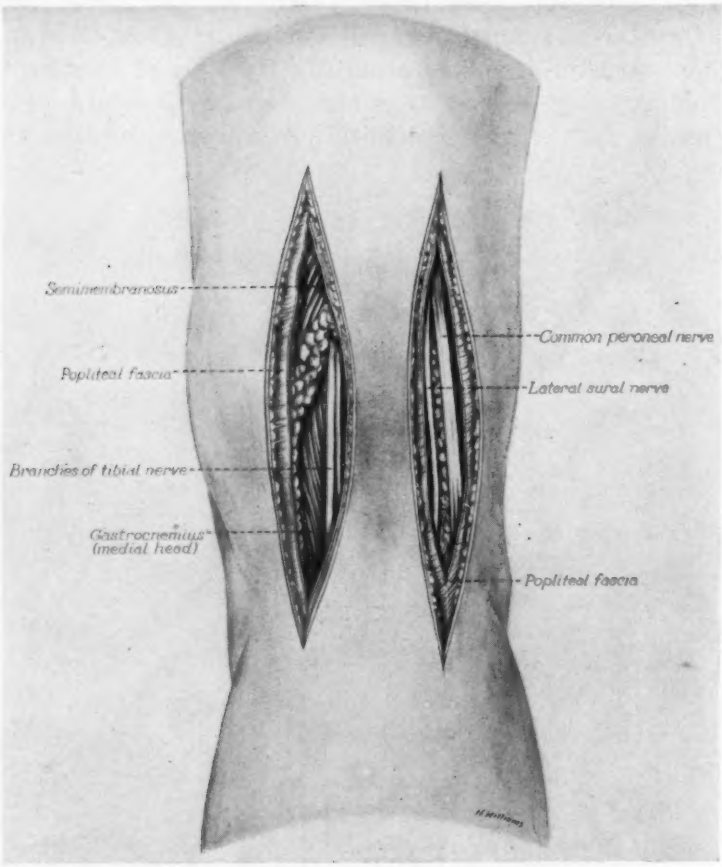

Fig. 2*B*.—For legend see page 749.

Hence the question of which tissues are contracted has to be answered at the operation, which should be undertaken with the idea that the procedure will be determined by the individual findings and will be as conservative as is consistent with good functional results. When the contracture is extra-articular, usually with flexion deformity of less than 45 degrees, tenotomy of the hamstrings ordinarily is sufficient. A lateral approach is made just medial to the biceps tendon over the course of the peroneal nerve. The medial incision is slightly to the inner side of the midline of the popliteal space and the tibial nerve and branches (Figs. 2, 3, and 4). This gives a thorough exposure of the posterior portion of the knee and at the same time brings into view the popliteal

nerves and arteries. One after another of the layers of tissue are divided, depending on the results. If the hamstrings have been divided without releasing the contracture, then the popliteal fascia is thoroughly exposed and divided, even that portion which forms the intramuscular septa. In most instances it also is necessary to separate the heads of the gastrocnemius. This proves sufficient in the majority of cases and it is not necessary to do a capsuloplasty.

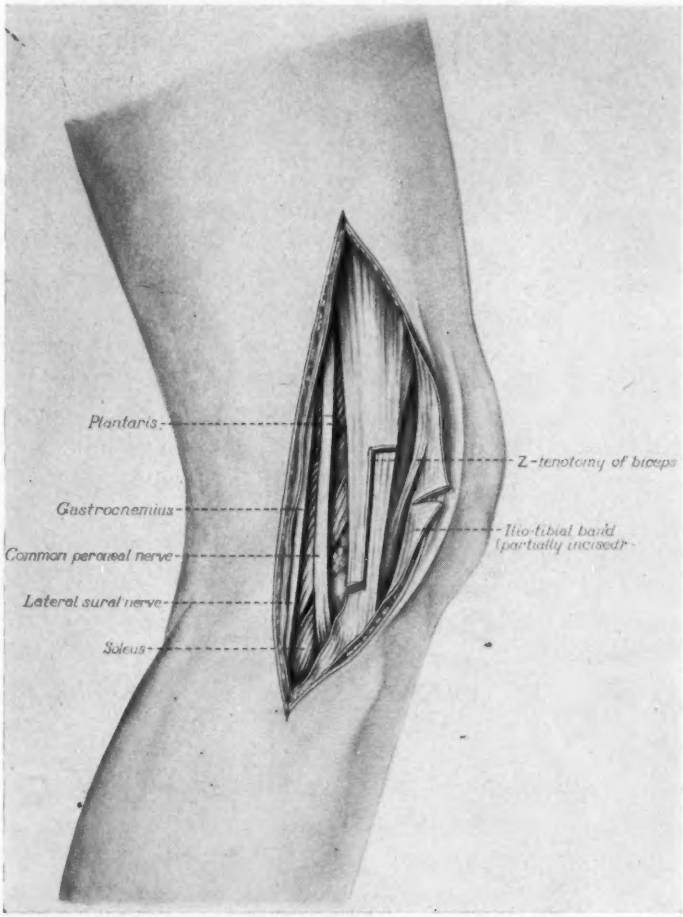

Fig. 3.—Lateral incision showing tenotomy of the biceps tendon, incision of the iliotibial band and exposure of the peroneal nerve.

In those cases in which fasciotomy is ineffective in releasing the contracture, a capsuloplasty is performed, according to Wilson's technique. In atrophic arthritis, where there usually is marked osteoporosis, sharp dissection is preferable to periosteal stripping. If the flexion deformity is not completely overcome by this procedure, we agree with Silver that the knee should not be forcibly extended, because of the danger of fracture, of subluxation, of exacerbation of inflammation, and of injury to the nerves and arteries. The warning frequently has been sounded

that excessive force applied in manipulation may cause postoperative fractures because of the atrophic condition of the bones. In some of Wilson's early cases in which complete extension was secured at operation, there was evidence of injury to the nerves. In later cases, he obviated this complication by taking care to free the nerve from the surrounding tissues for a considerable distance. In extreme contractures

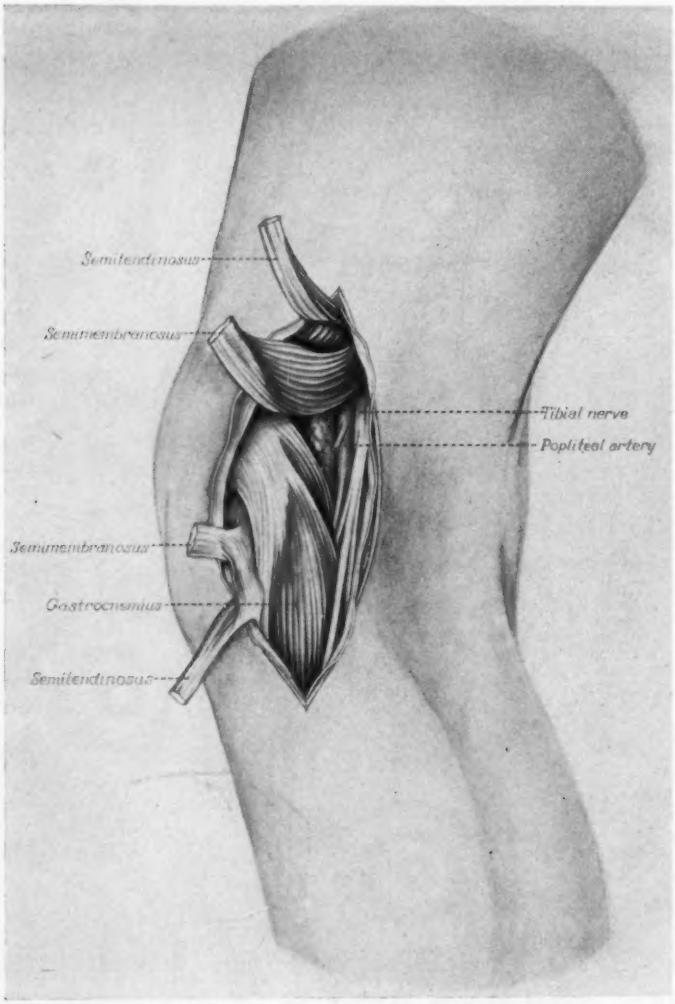

Fig. 4.—Medial incision showing semimembranosus and semitendinosus tenotomized tibial nerve and popliteal artery and inner head of the gastrocnemius exposed.

it must be remembered that the danger of injuring the nerves and vessels at operation is increased because they may be displaced from their normal positions or imbedded in scar tissue, making their identification difficult.

In those instances where tenotomy, fasciotomy, and capsuloplasty are contraindicated because of excessive flexion deformity, where these procedures may result in damage to nerves and blood vessels, or where

ankylosis of the joint is impending, osteotomy either above or below the knee joint to correct the deformity is the method of choice.

The operation is considered satisfactory when extension has been corrected to within 15 degrees of normal. Additional extension usually is secured by the postoperative application of traction and by physical therapy, consisting of heat, massage, passive exercise, and muscle setting. Our practice is to employ Russell traction for extension because that affords a certain degree of extension to the upper portion of the tibia while producing traction which eliminates a backward luxation of the tibia in the knee joint. Various other apparatus, based on similar mechanical principles, have been proposed to aid extension of the joint, so the type of traction used becomes a matter of individual choice. Skeletal traction has been advocated by a number of authorities, but we have not used it, largely because of the dangers involved in inserting a pin into atrophic bones, and because the methods used to increase extension have been satisfactory.

Synovial hypertrophy is common in cases of flexion deformities of the knees, particularly in those with intra-articular lesions. In a number of instances, it has appeared that this would be an obstacle to adequate extension of the joint, and plans have been made for a synovectomy following a period of rest and traction. However, in none of these cases has synovectomy proved necessary because the synovitis subsided satisfactorily during the postoperative period while the patient was at rest. Magnuson[7] also has noted that removal of the synovia has not been necessary in his cases subjected to joint débridement. In this connection, it is interesting that Steindler (as quoted by Kulowski[5]) has called attention to hypertrophy of the infrapatellar fat pad as a primary cause of flexion deformity and an anterior mechanical block to extension.

CONCLUSION

It is important to emphasize that the conservative viewpoint should be carried through to the evaluation of the results of treatment. In many instances, the patient cannot be rehabilitated to the extent that he regains normal function of the knee joint. But if enough function can be restored to enable him to move about, even with crutches, rather than to be completely bedridden, a great deal has been accomplished, both from the standpoint of the patient and from the standpoint of society.

Experience has shown that by keeping in mind the structure of the knee joint and the nature of the disease process resulting in flexion contracture, it is possible to rehabilitate these patients satisfactorily without resorting to the radical procedure of capsuloplasty in the majority of cases. When tenotomy does not suffice, fasciotomy does, as a rule, and except in the rare cases in which the condition is most advanced, the capsule may be left intact. These more conservative procedures naturally carry less risk of infection, increased stiffness and other

complications, shorten the period of convalescence, and hence are distinctly preferable from the standpoint of patient, surgeon, and hospital.

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CHRONIC EMPYEMA DUE TO DERMOID TUMORS OF THE MEDIASTINUM

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THE causes of chronicity in empyema thoracis have been listed as: inadequate drainage, presence of foreign bodies, communication with the lung, cavities that cannot be spontaneously obliterated, and tuberculosis or fungus infections. I should like to emphasize a sixth cause—dermoid tumors of the mediastinum.

Dermoid tumors of the mediastinum are called epidermoids when derived from ectodermal elements, true dermoids when there is in addition evidence of mesodermal derivation, and teratoma when derivatives of all three germinal layers are present.[1]

Secondary infection sometimes constitutes a deceiving as well as a dangerous complication of these neoplasms and leads to masking their presence behind the clinical syndrome of chronic empyema. Infection usually occurs from rupture into the neighboring pulmonary parenchyma or bronchi due to pressure. Suppurative pleurisy may result which, even when adequately drained, will not be permanently cured because of the underlying pathologic process. Since this fact seems to need emphasis, the following strikingly similar case histories are presented.

CASE REPORTS

CASE 1.—J. B. is a young woman 28 years of age. In 1917, at the age of 5 years, she had what was diagnosed as pneumonia of the right lung with subsequent empyema which was treated by tube drainage. A sinus persisted which continued to discharge purulent material, despite which the patient remained quite well. This sinus was closed in 1923 when the patient was 12 years of age. For two years she coughed up the same type of material which had come from her external thoracic opening. She failed to improve during this time, so the tract was reopened in 1925. In attempts to eradicate what was thought to be a chronic empyema cavity, thoracoplastic procedures were carried out in 1928 and again in 1931. It was at this later time that sebaceous material and hair were found at a postoperative dressing of the wound. More of the same substance was removed and on three occasions radium was used to destroy the cyst wall without success. In 1932, a tumor was removed from the right chest weighing 292 Gm.; it contained bone, lymphoid tissue, stratified squamous epithelium, sebaceous glands, and connective tissue. In 1934, residual bronchial fistulas were closed successfully. Two years before removal of the thoracic tumor this patient complained of aching joints associated with swelling. Except for a continuation of this complaint to a lesser degree she is in good health. She has no symptoms referable to her chest, except slight dyspnea on exertion.

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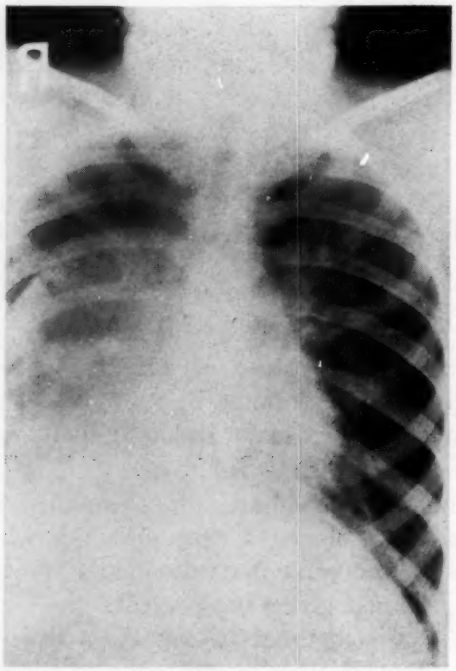

Fig. 1 (Case 1).—Roentgenogram of chest showing density in right lower median lung field.

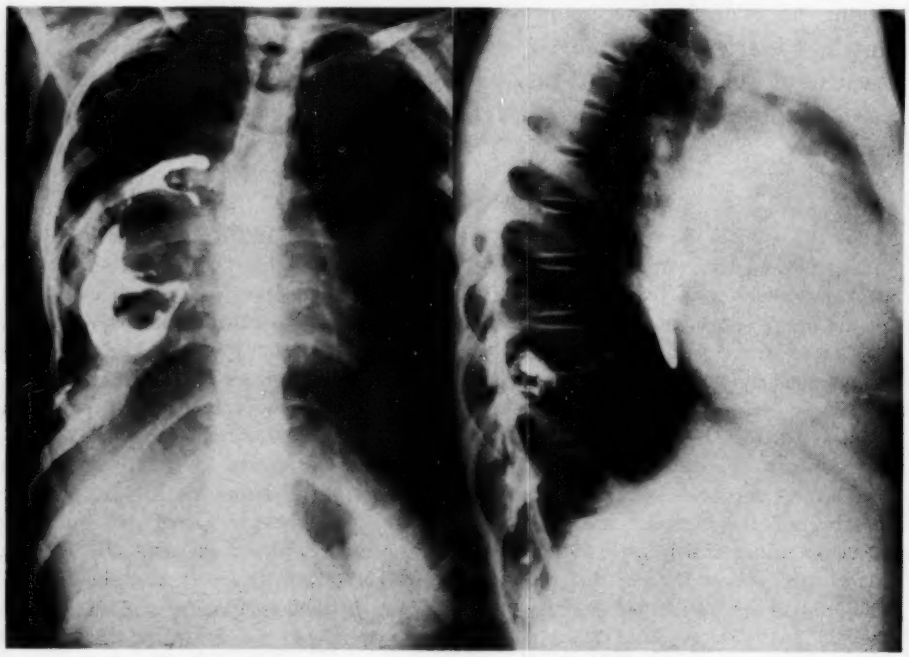

Fig. 2. Fig. 3.

Fig. 2 (Case 1).—Lipiodol visualization of sinus tract. This and accompanying lateral view clearly demonstrate the anterior location of the lesion.

Fig. 3 (Case 1).—Lateral view of lipiodol visualization.

Fig. 4.—Photograph of gross specimen of dermoid tumor surgically removed. Note the hair characteristic of these tumors.

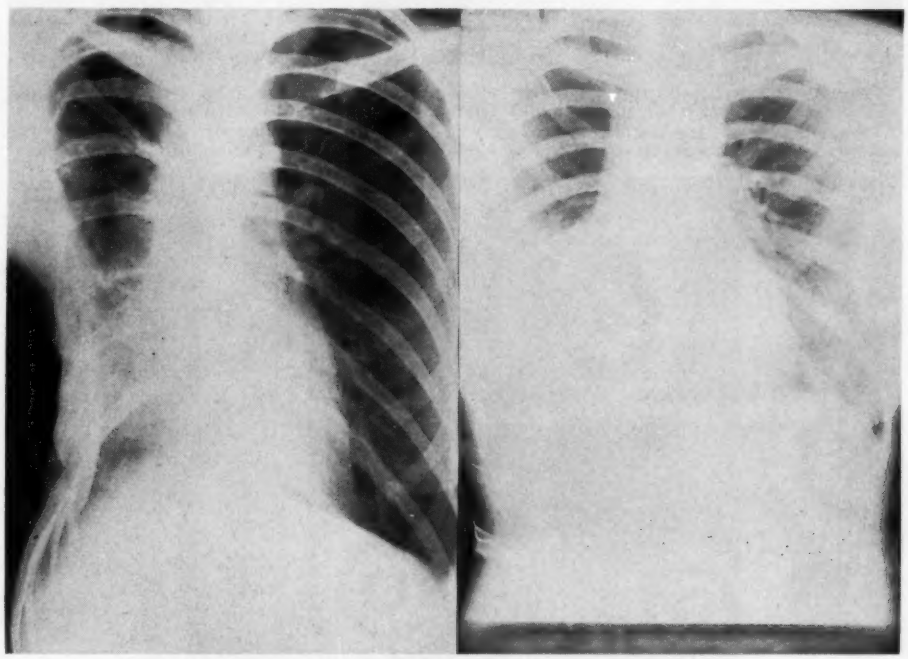

Fig. 5. Fig. 6.

Fig. 5 (Case 1).—Postoperative roentgenogram of chest. There is considerable thoracic deformity because the patient had been treated for chronic empyema for many years before diagnosis of tumor was made.

Fig. 6 (Case 2).—Roentgenogram of chest showing density in right lower median lung field, as in Case 1.

CASE 2.—S. A. is 30 years of age. Although it is difficult to obtain a clear picture of her earlier complaints, there is definite evidence of some thoracic disorder associated with severe cough and expectoration of green, purulent sputum as early as

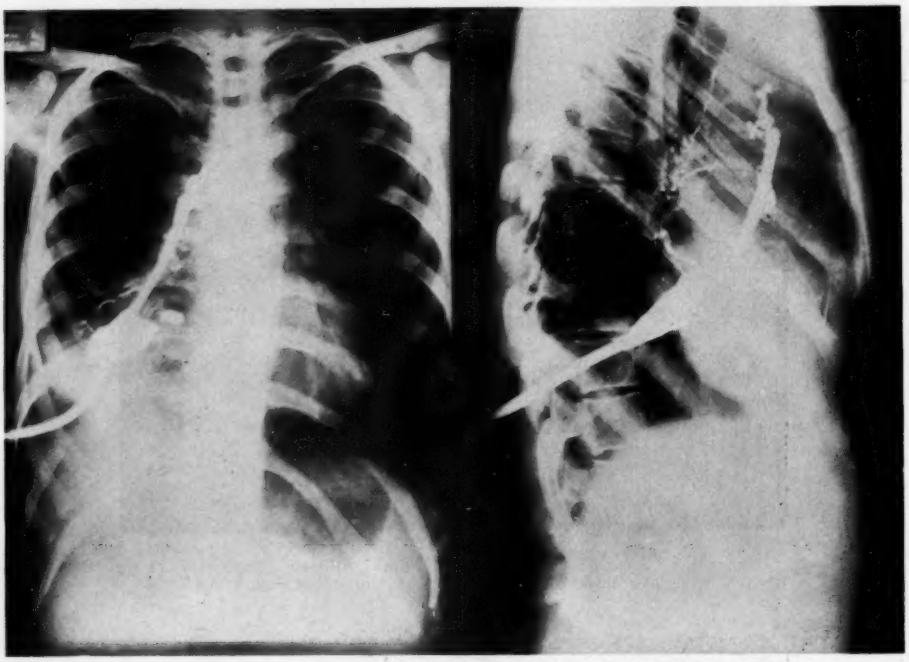

Fig. 7. Fig. 8.

Fig. 7 (Case 2).—Anteroposterior view with catheter in sinus tract for lipiodol visualization. Notice oil in bronchial tree indicating the presence of fistula.

Fig. 8 (Case 2).—Lateral view of Fig. 7, which conclusively demonstrates the lesion to be in anterior mediastinum. Costovertebral gutter region is clear.

Fig. 9.—Photograph of tumor removed, showing hair on its surface.

six years ago. In the summer of 1938, there developed, in addition to the productive cough, pain behind the sternum. A physician was consulted who found purulent fluid on aspiration of the right chest posteriorly. Tube drainage was instituted and was continued until July, 1939.

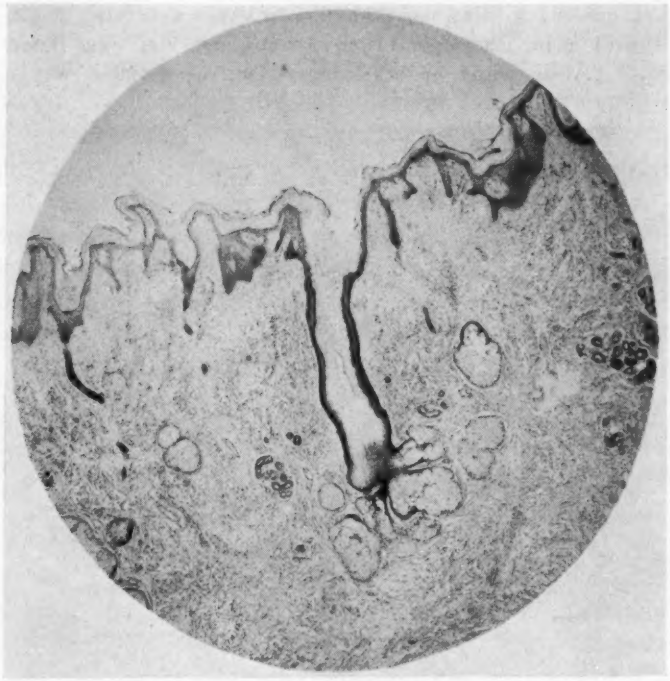

Fig. 10.—Low-power photomicrograph of tumor showing ectodermal and mesodermal derivatives.

Fig. 11.—Postoperative wound with moderate deformity. This may be improved later by covering with the breast.

At this time she came to Presbyterian Hospital. Because she had a septic temperature the posterior sinus tract was opened more widely to promote adequate drainage. A tentative diagnosis was made of chronic empyema. Since her fever did not entirely subside, two months later a second operation was carried out to unroof the chronic empyema cavity. The sinus was found to extend far forward and at its anterior end a white movable mass was seen and felt. A piece of tissue was secured with a bronchoscopic biting forceps and histologic report was "sebaceous cyst." A diagnosis of anterior mediastinal dermoid was made. The

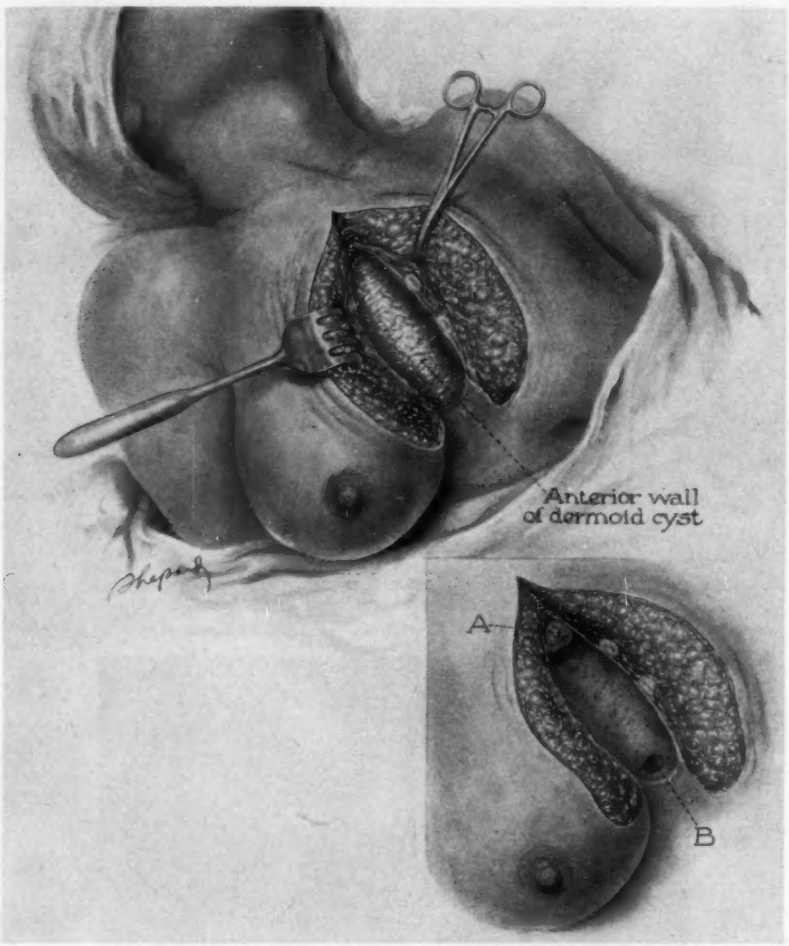

Fig. 12.—Upper illustration is that of the capsule surrounding the actual tumor. Within this was contained the purulent sebaceous fluid which drained from the posterolateral sinus whose anterior communication is shown at *B*; *A* marks the upper end of the tumor before its complete removal.

tumor was removed in two stages through an anterior thoracic approach. Since that time cholecystectomy has been performed for gallstones which were visualized in studying the thorax. These had produced severe colic on two occasions. The patient has gained twenty-five pounds in weight and is quite well.

DISCUSSION

It is only by carefully planned study that diagnosis of the underlying cause of chronic thoracic sinuses can be correctly made. In ad-

dition to thorough general physical examination, specific investigation of the thorax must be carried out. The sputum and sinus discharges should be searched for tubercle bacilli, as well as for fungi of all types. Culture is made of both, as well as direct smear for hair, sebaceous material, cholesterin crystals, and epidermis. Guinea pig inoculation is advised.

Roentgen examination is made in both the anteroposterior and lateral views before and after the sinus is visualized by the injection of lipiodol or brominol. Fluoroscopy of the stomach and colon to rule out diaphragmatic hernia through the foramen of Morgagni is suggested. Wassermann and other tests for syphilis should be performed routinely. Aneurysm has been confused with tumor[2] and, of course, may lead to disaster if unrecognized. Bronchoscopy, and even endoscopic examination of the sinus, may confirm a tentative diagnosis if hair, cholesterin, etc., are found.

Characteristically, dermoids are found in the anterior mediastinum, extending laterally and posteriorly as they enlarge. A study particularly of the lateral roentgenograms of the chest in the cases presented shows the costovertebral gutter region to be free from disease. This is usually involved in a chronic empyema process. Lipiodol visualization of the sinus tracts demonstrates their extension into the anterior mediastinum. This suggests the diagnosis of dermoid tumor, which was further substantiated in each case by obtaining material from the sinus which was characteristic of these lesions, such as hair and sebaceous material.

At operation in each instance a tumor was removed. Hair can be seen on both specimens (Figs. 4 and 9). The derivatives of ectoderm and mesoderm can be seen on microscopic section (Fig. 10).

It is not the purpose of this paper to discuss the surgical treatment of mediastinal dermoids. Infection has been largely responsible for mortality in the reported operative deaths.

The surgical approach to each patient must be individualized. While the transpleural operation through a posterolateral incision as advocated by Harrington[3] affords the best exposure, and thereby facilitates careful dissection from other mediastinal structures, the anterior approach may be safer in the presence of infection. Because of the malignant changes in at least 15 per cent of these tumors, early surgical removal is advised.

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Editorial

Recognition of Military Training as a Determination of Eligibility for American Boards

MANY of the younger men in the service have been concerned about the effect which the war would have upon their eligibility for the various American Boards. Whereas many men have previously outlined a course of formal surgical training which would make them eligible to take their respective board examinations, with the introduction of the United States into the war and the necessity of their enlistment in the Armed Forces, this formal training has necessarily been interfered with. It has been the hope of those interested in graduate medical training that recognition could be given for adequate training received in the Armed Forces.

It is significant that the American Board of Orthopedic Surgery, one of the oldest boards, has taken formal action concerning this. "In order that the committee on eligibility may have adequate data for evaluation of the training of applicants who have served with the Armed Forces, a plan will be set up whereby all who are assigned to orthopedic services will be provided with an orthopedic service record. These records must indicate the character and amount of orthopedic work performed at each post to which prospective applicants are assigned. The notations of each officer concerning his service at each post must be signed by his superior officer in charge of the orthopedic service and approved by the commanding officer. The orthopedic service record will be retained by the officer and finally will be submitted with his application to the Board for review by the committee on eligibility."

It is probable that other boards will follow the lead taken by the American Board of Orthopedic Surgery and set up similar plans because in this way it will be possible for the man getting adequate training to have this designated at the time he is getting it so that proper evaluation can be made whenever he makes application to take his examination. Because of the new ruling by the American Board of Orthopedic Surgery and because of the possibility of such a ruling being made by other boards, it is desirable that anyone contemplating taking examinations for the various boards should communicate with his respective board at the earliest possible moment in order that he may get information concerning the service record.

The American Board of Orthopedic Surgery has also decided that in the future examinations will be given in two parts. Applicants who have completed a rotating internship and one or two years of resident training in orthopedics or their equivalent in military surgery will be eligible for Part I of the examination. This part will cover the basic sciences, the fundamentals of surgery, elementary principles of orthopedic and fracture treatment, oral interviews, and written examinations. Tentative plans provide that Part I may be given during the fall months in four different centers, probably New York, Chicago, New Orleans, and San Francisco. Part II of the examinations will probably be given only once a year as heretofore, in connection with the meeting of the American Academy of Orthopedic Surgeons. Applicants for Part II must have completed their full requirements for eligibility including their practice periods. A written examination on all interviews will include advance operative technique, standard orthopedic procedures, reviews of the literature, case records, et cetera.

—*Alton Ochsner, M.D.*
New Orleans, La.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PROBLEMS OF INFANTILE PYLORIC STENOSIS WITH PARTICULAR REFERENCE TO SURGICAL TREATMENT

A SURVEY OF THE PERTINENT LITERATURE AND A CLINICAL ANALYSIS OF THIRTY-FOUR CASES

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WHEN a disease has ceased to be a therapeutic problem, scientific interest in it is likely to wane. Not infrequently successful measures of treatment are devised before the fundamental problems of a disease have been solved, and in such instances the consequent lack of interest will be reflected in the neglect of the related, less practical but basically important, questions.

The present status of infantile pyloric stenosis is a good example in point. Since its surgical treatment achieved an unexcelled success, the disease has gradually passed into a relative scientific obscurity, particularly in the United States, where the therapeutic results have been perhaps the most brilliant. And yet many fundamental problems of the disease have remained unsolved. Nor will the answer to these questions come unless curiosity and interest are kept alive in the laboratory and in the sick ward.

An assessment of our stock of knowledge and a synthesis of the picture of the disease in modern light seem, therefore, both timely and profitable, particularly since during the past twenty years only two surveys of the disease with an attempt at comprehensiveness have appeared in the English language (Romano and McFetridge, and Sauer). The present study will endeavor to summarize the modern concept of the disease, the historical development and current state of the problems of its causation, natural history, and treatment, on grounds of the pertinent literature and a series of clinically analyzed cases.

Nomenclature.—In the medical literature of English-speaking countries pyloric stenosis of infancy has become known in association with the adjectives congenital and hypertrophic. The term congenital is objectionable since the problem of the congenital nature of the disease

is by no means settled. Hypertrophic is redundant, for there is no other than hypertrophic kind of infantile pyloric stenosis. The latter term, that is, infantile pyloric stenosis (also employed in the title), appears to be the most precise. In German the equivalents of pylorospasm and pyloric stenosis are used interchangeably, while in English stenosis always denotes organic obstruction. The French, too, clearly distinguish between pylorospasm and pyloric stenosis, reserving the term pseudostenose for the former. The other Latin countries follow the French usage, while the Scandinavians and Central-Europeans copy the German example. In the older literature the designations of *stenosis pylori congenita* and *hyperemesis lactentium* are encountered.

In addition to these standard designations, one meets a host of loosely coined sporadic names, such as pyloric contracture, congenital pyloric spasm, essential pylorospasm, spastic stenosis, pylorostenosis, pyloric stenosis of infants, muscular hypertrophic pyloric stenosis, stenosing pyloric hypertrophy, and *maladie pylorique*.

HISTORY

Scattered accounts of cases closely corresponding to the entity now known as infantile pyloric stenosis were published as early as the seventeenth century. Kellett believes that the case report of Hildanus, a famous German pediatrician who flourished in the second half of the seventeenth century, should be accepted as an example of this disease; the date of the first description would thus be 1646. While this claim may be questioned, there is little doubt that the accounts of Blair (1717), C. Weber (1758), and Armstrong (1771) are strikingly characteristic of the disease as now recognized. The case observed by Hezekiah Beardsley has several distinctions: it appeared (1788) in the first medical periodical published in the United States; it was discovered and made public again by Sir William Osler; and for many years it was believed to be the earliest example of the disease then extant. In the early nineteenth century Pauli (1839) and Williamson (1841) made accurate independent observations of this condition, and Dawosky (1842) for the first time described the projectile character of the vomiting.

Considering the very typical clinical manifestations of the disease, the meagerness of the number of these reports is surprising and hardly explicable by the rarity of the disease alone. The very deplorable state of pediatrics, the general ignorance and even indifference in the matters of infant disease offer a more likely explanation. But even the few early reports made no impression whatever on contemporary medical thought. Children with hypertrophic pyloric stenosis continued to die with the disease undiagnosed and, what was more important, untreated. In fact, the original case reports were so completely covered with the dust of oblivion that they had to be rediscovered in the twentieth century, when the disease had long been well recognized in most of its aspects.

Thus when, in 1887, at the Wiesbaden meeting of the Gesellschaft für Kinderheilkunde, Hirschsprung described two cases of infantile pyloric stenosis, he in fact presented a new disease as far as the practitioners of medicine in attendance were concerned. Hirschsprung's interest was mainly in the anatomic aspect of the disease, his attention having been brought to the problem by the reports of Landauer (1879) and Mayer (1885) dealing with the pathology of hypertrophic pyloric stenosis in the adult. He gave an excellent account of the gross pathologic changes and expressed the supposition that these alterations were the cause of a definite clinical form of infantile vomiting. He further assumed that the adult type of hypertrophic pyloric stenosis originates from the infantile form—a question not yet answered even today. (See Elmer and Boylan, Frank, Judd and Thompson, McNamee, Rössle, McClure, Twining.)

Within a brief time after Hirschsprung's presentation the disease became widely known. The eagerness of the prodigiously growing medical science at the turn of the century quickly engulfed the new problem about which a large literature soon grew up. Finkelstein (first to describe the palpable pyloric tumor), Huebner and Pfaundler in Germany, Hutchinson and Thomson in England, and Holt, Downes, and Scudder in the United States, were especially eminent among those who early interested themselves in the disease.

The Typical Clinical Picture.—As a convenient reference, the picture of the disease as ordinarily manifested—an abstract model of the disease, so to speak—may be here given. The typical infant is a lusty male child, probably the first child of the family, born spontaneously after a normal prenatal development. He nurses well and shows good progress until his third week of life when, rather suddenly, he begins to vomit some of his feedings. While maintaining his appetite, and without developing a febrile disease, his vomiting becomes gradually more severe, be begins to lose weight, becomes wizened and, unless energetic medical attention intervenes, dies of starvation or pneumonia before reaching the age of three months.

PATHOLOGY

The pathologic anatomy of the disease is simple and clear-cut. All the essential alterations encountered are confined to the stomach and, in particular, to the pyloric canal (*canalis pyloricus sive egestorius*). The general wasting of the body and the pathologic processes developing terminally are secondary to starvation and in no way restricted to the disease.

The entire pyloro-antral region shows a shining, gray-white spindle-shaped thickening of cartilagenous consistency. The length of this swelling (loosely called tumor) is 2 to 3.5 cm. and its width 1.5 to 2 cm. with a wall thickness of 0.5 to 0.8 cm. Almost without exception (Arreger, Chiari, Rothschild, Wernstedt) the mucosa appears normal aside from

the changes of catarrhal gastritis frequently present as a secondary phenomenon. Inconsequential mucosal erosions may be found but true chronic ulcers have been described as great rarities (Kleinschmidt, and Thompson and Gaisford). The muscular coat of the entire stomach wall is also thickened to a lesser or greater degree and the lumen of the viscus may be considerably dilated. It is generally agreed that microscopically the increase in the volume of the pyloric musculature is due to a true hypertrophy; that is, there is an increase in the size of the component muscle cells without an increase in their number. (v. Mettenheim, on the other hand, states that the process is both a hypertrophy and a hyperplasia.) The inner, circular fibers are primarily involved, although the longitudinal layer also shows a lesser degree of similar alteration. The latter is usually $\frac{1}{6}$ to $\frac{1}{4}$ the thickness of the circular muscle coat (Balan) whose diameter, in turn, varies between 3 and 7 mm. (3 to 4 times normal) (Wollstein). While the connective tissue substance of the muscle coat also shows some increase in volume, this does not materially add to the formation of the pyloric swelling (as originally held by Hirschsprung, and Finkelstein and his associates).

Balan and later Cameron made the very significant observation that the elastic fibers of the submucosa and, to a lesser degree, of the muscularis mucosae and muscularis propria also partake of the process of hypertrophy and that this hypertrophy, together with the muscular hypertrophy, is limited to the pyloric canal (leaving the pyloric ring itself uninvolved) and is a progressive change, becoming more pronounced with the lengthening of the duration of symptoms, advancing in the long axis of the canal both orad and aborad.

The increase of muscle volume within the confinement of an adherent and unstretchable peritoneal covering transforms the limp and relaxed pyloric canal into a hard and solid tube. Another effect of the muscle swelling is the protrusion of the thickened pyloric segment into the duodenal lumen, much as the cervix intrudes into the vagina. The tension within the thickened pyloric muscular coat compresses the vascular branches and lends a pale, bloodless appearance to the component tissue. The consistency of the muscle turns crisp and gritty, but as the disease progresses, presumably on account of the stretching and loosening of the peritoneal covering by its growth, it again becomes softer and more vascular. It is this factor of age that apparently accounts for the two distinct types of pyloric tumor described by some authors (Heile).

There is a considerable body of evidence, based on observations in vivo, to show that the pyloric tumor undergoes a cycle of changes grossly visible and palpable. It apparently reaches its maximum hardness and size between the fourth and ninth postnatal weeks. Thereafter, it tends to become softer of consistency and smaller in extent (Higgins and Tallerman). Whatever the underlying cause, these cyclic alterations are in harmony with the modern views of pathogenesis and throw light

upon the anatomic basis of the clinical observations that the disease, once past the first three months of life, shows an inclination to spontaneous healing.

The blunt projecting end of the hypertrophic pylorus creates certain anatomic relationships that are of practical importance. The apex of the fornix created all around this stopperlike mass and consisting of the duodenal mucosa becomes bound down to the muscular and serosal coats, forming the so-called "zone of adhesions" (Browne). Separation of the various layers at this point, therefore, becomes difficult and may cause technical mishaps at time of operation.

More recently degenerative changes of the plexus of Auerbach in the wall of the pyloric canal and stomach have been described (Herbst). The possible significance of this finding will be touched upon later.

ETIOLOGY AND PATHOGENESIS

The question of the causation of infantile pyloric stenosis has been a matter of extended speculation and has not as yet been accurately answered. In the following, the various known etiologic factors and the purely theoretic systems of pathogenesis, for the sake of clearer organization, will be discussed under separate headings.

ETIOLOGIC FACTORS

Genetic (Hereditary) Factor.—Genetic research in cases of infantile pyloric stenosis is only at its very beginning but already a considerable body of observations has been accumulated.

The most commonly appreciated evidence of heredity in a disease is its familial occurrence. Infantile stenosis was observed to occur in two siblings by Bousquet, Carstens, Cockayne (twice), Grisson, Hammond, Lereboullet (thrice), Pouyanne, Reuben (twice), Richter, Sauer (twice), Stenström (twice), Suner, Svensgaard (thrice), Thompson, Tribble, Uhr (four times); in three siblings by Bratusch-Marrain, Gorter, Halbertsma, Henschel, Kehl and Thomann, McGregor, Péhu, Schippers and van der Molen, Svensgaard; and in four siblings by Finkelstein, Ashby and Southam, Thomson, Carstens.

Fabricius reported the case of a family in which three children born of a mother and her first husband, and a fourth child born of the same mother and her second husband were affected. In Caulfield's case father, daughter, and son evidenced the disease. The occurrence in father, son and possibly grandson was mentioned by Schreiber; in father and son by Svensgaard and Schmid; in father, son, and father's brother by Pouyanne; in father and two sons by Lereboullet; in mother and son by Ashton; and in uncle and nephew by Schmid.

Halbertsma gives the distribution of five instances of the disease in the families of two brothers. The pedigree published by Brendle is of the greatest interest; he discovered nine cases in four families interrelated in such a manner that one case each occurred in the four sons of three sisters whose five brothers had been suffering from the disease.

For an accurate statistical evaluation of the frequency of familial occurrence one should possess the knowledge of the total number of observations of the disease among which the examples of consanguinity were detected, or, conversely, the presence or absence of familial tendency in the highest possible proportion of the observed and reported instances of the disease. Only the latter information is available, and that but on a small scale. Monrad noted 7 instances of familial occurrence in 174 cases; Uhr, 4 in 47 cases; Rinvik, 10 in 107 cases; Still, 4 in 248; Thompson and Gaisford, 2 in 209; Strauss, 2 in 221; and Lereboullet, 3 in 47 cases. Even if the statistical significance of these sporadic and incomplete data cannot be expressed numerically, they appear to make the assumption a reasonable one that, as judged by the frequency of familial incidence, a genetic factor probably plays a role in the etiology of infantile pyloric stenosis.

A further valuable criterion of the presence of hereditary influences is the incidence of the disease in twins. Numerous such observations have been recorded. Simultaneous presence of the disease in each of a pair of monozygotic (identical) twins was described by Bilderback, Card, Davis, Ford and co-workers (twice), Gelder, Halbertsma, DeLange, Lanz, Moore, Redgate, Redlin, Sheldon, Sommer, Varden. Similar occurrence in fraternal twins was noted by Monrad (twice) and Wallgren (twice). One of a pair of paternal twins showed the disease in the cases reported by Halbertsma, Knauer, McKechnie, Schmid, Thomson, Wallgren (two cases). In the case of uniovular twins, as a rule both are affected; in binovular pairs one of the pair is usually free from the disease. Although Lasch and Lereboullet reported one pair of monozygotic twins, each, with one of the pair unaffected, there is serious doubt of the monovular character of these instances. The largest collection of cases of twinning is that of Sheldon who was able to investigate the records of thirty-six sets of twins.

Concerning the frequency of twinning among infants with pyloric stenosis, Ford and his associates observed 11 pairs of twins among 436 such patients (1:36.3); Rinvik, 2 among 137 (1:68.5); Pouyanne, 1 among 35 cases (1:35); Monrad, 3 among 223 cases (1:76.5); and, finally, in 1000 collected cases Sheldon found the ratio of twinning to be 1:43.4 (the normal ratio being 1:80). The total number of cases analyzed is again too small to make statistical conclusions certain. It seems logical, however, to subscribe to Sheldon's opinion that the evidence of twinning incidence is a strong proof that pyloric stenosis of the infant has a genetic basis. It must be added that from the information now available the exact mode of inheritance of the hereditary factor cannot be stated. It does not appear to be entirely sex-linked, however, and it is apparently complemented by an environmental factor (Cockayne and Sheldon).

Closely allied to the problem of hereditary factors is the much debated question of the presence of a constitutional anlage. Attempts

have been made to ascertain constitutional patterns in the parents as well as in the infants, or to be more precise, since such investigations of infants are difficult, in children with past history of pyloric stenosis. The results have been highly contradictory. Reiche, Behrmann, Block, and others believe they have demonstrated definite constitutional stigmas in the parental group in the form of "gastroneuropathic tendencies." Cohen and Breitbart found in 44 per cent of 27 cases allergic heredity or allergic symptoms. v. Mettenheim considers the majority of these infants to belong to a "neuropathic-asthenic" constitutional type; he also finds them often to evidence certain uniform physical traits, such as hirsutism and prominent eyes. Others (Lehmann and Bau) deny the significance or even presence of demonstrable constitutional factors.

The *intrauterine development* of the infants with pyloric stenosis shows no significant deviation from normal. Prematurity has been found with the usual frequency (Rinvik 5.8 per cent and Strauss 1.5 per cent) and the course of pregnancies has revealed nothing unusual (Strauss and Rinvik). Abnormal deliveries occur as often as generally expected (Nissen and Boecker, Strauss).

It has been long known that infantile pyloric stenosis *occurs predominantly in the first-born infant.* While the variation in the percentages of incidence reported is great (46 to 80 per cent; Barrington-Ward, Bodart and Mathieu, Faxen, McLeod, Rinvik, Robertson, Still), the average lies between 50 and 60 per cent. The frequency of first births in the general population is below or just around 40 per cent of all recorded births (Ford and associates, Salmi, Wallace and Wevill). A convenient way of comparing the available figures is to divide all births into two groups: first births and births of an order higher than first. Thus we obtain the following figures: Wallace and Wevill: first births among patients with infantile pyloric stenosis 55.6 per cent, in the general population 20 per cent; the values given by Salmi and by Robertson are as follows: 58.6 per cent and 42.5 per cent, and 51.8 per cent and 41.2 per cent, respectively. Thus the conclusion seems sound that the absolute preponderance of first-born infants among those suffering from pyloric stenosis is real. After a closely reasoned statistical analysis Ford and co-workers reached the same conclusion. Thus far, however, no plausible ideas have been advanced for the explanation of this phenomenon.

Another generally recognized finding is the overwhelming *predominance of males* among these patients. The proportions given range from 72.9 to 100 per cent (Bodley, Brown, Donovan, Fredet, Kehl and Thomann, Ladd, Lanman and Mahoney, McGahee, McLeod, Meredith, Mouriquand and Weill, Munting, Ochsenius, Oehler, Paas, Pouyanne, Raisch, Rinvik, Robertson, Schönbauer, Still, Strachauer, Strauss, Tallerman, Vanden Berg, Wiedhopf and Bruhl) with the average between 85 and 90 per cent. It will be noted presently that this fact has been incorporated into the framework of some of the theories of pathogenesis

(Stolte and Ernberg). Some authors claim, but without adequate statistical evidence, that when it occurs in the female the disease has a tendency to be particularly severe.

The *racial distribution* of the disease has been very little studied. Lanman and Mahoney found no evidence of influence of racial factors in their cases. Direct facts to the contrary are hard to find indeed. It is very evident, however, to anyone studying the literature of the disease, that case reports from certain countries are very scarce. For instance, from Italy only 45 cases were recorded in the literature until 1935 (Colarizi). With the exception of France (Morlet, Mutel and Rémy, etc.), the same trend is found in all the other so-called Latin countries (Arquellada, Giustinian and Antonelli, Zuviria). It is, of course, true that many factors other than lack of racial affinity may lead to a meager number of cases observed and reported in any one country, but this disparity is so marked that the conclusion is almost inescapable that the Anglo-Saxon races for some reason are much more susceptible to the disease. Moreover, very few cases have been observed in Negroes (Davison) (Donovan, about 2 per cent of all cases in New York; McGahee, 2.1 per cent in St. Louis). Heile encountered a high incidence among Jews. It has also been stated that some *geographic influence* may have a role: the Alpine regions of Europe appear to be entirely free from the disease (Ramstedt).

Bayer was the first to suggest a *seasonal variation* in the incidence of the disease. He found that a considerably larger number of cases was treated during the spring quarter of the year. This variation in frequency has been attributed to changes in the diet (vitamins), enhanced endocrine activity, or hypersensitivity of the vegetative nervous system, all incidental to the changes of season (v. Mettenheim). Schönbauer and McGahee recorded similar observations, but Faxen, Wiedhopf and Bruhl, Svensgaard and others could not corroborate this assertion. The weight of evidence is certainly in favor of the absence of seasonal influence on the occurrence of the disease.

Some authors (Stolte) attempt to attach great significance to the marked *preponderance of babies who have been breast fed.* The frequency of breast feeding indeed varies from 65 to 75 per cent, but upon closer scrutiny one sees that this is about the number of infants that are breast fed normally in the age group in which pyloric stenosis is prone to appear (Behrmann, Faxen, Monrad, Salmi).

Upon analyzing our own material for the presence or absence of the factors just discussed, we find that no familial tendency can be discerned. The proportion of males is 85.3 per cent. All but three of the patients belonged to the Anglo-Saxon race, there having been in addition a Hungarian, a Polander, and a Russian. Fifty-eight per cent of the infants studied were first born and 75.8 per cent of them were breast fed. In all these latter respects, therefore, our material repeated the trend generally observed. There was a slightly higher percentage of abnormal births (one face presentation, one vertex presentation, one foot-

ling breech, one delayed second stage, and one low cervical cesarean section—altogether 16 per cent) than usually found, but no prematurity was noted. As to the influence of season, our material shows how fallacious the apparent result of the study of a short series of observations may be: Fully 50 per cent of our cases had their onset in the months of July, August, and September, a wholly unique phenomenon and obviously without significance.

THEORIES OF PATHOGENESIS

Before a sufficiently large number of post-mortem examinations were done the theory was advanced that the obstruction of the pyloric outlet was caused by congenital anomalies: misplaced embryonic tissue rests, such as atopical pancreatic or duodenal glandular tissue (Torkel, Ribbert cit. by Schmid, and Lehmann). With the gradual accumulation of pathologic data and with the clarification of the typical picture of the anatomic alterations it became evident that these abnormalities, together with the embryonic adenomyoma of the pylorus occasionally encountered (Magnus-Alsleben), are but rare malformations that may cause symptoms resembling true pyloric stenosis but have no significance in its etiology.

The presence of congenital anomalies near the pyloric region and elsewhere in the body but concurrent with pyloric stenosis (palatoschisis, atresia ani, congenital heart disease, agenesia of fingers or teeth, and others; Lehmann) had, however, a decided influence on the theories that conceived the pyloric lesion as a *congenital malformation.* (We now know that the total number of these birth abnormalities is too small to have any statistical significance.) The appearance of the symptoms at an early date after birth or, in some cases, at birth, and the observation of the disease in premature infants also seemed to support a congenital etiologic mechanism. Thus Hirschsprung, Finkelstein, and Ibrahim established the theory that the pyloric tumor represented an arrested stage or a complete absence of the process of involution of the fetal pylorus; the abnormal musculature thus remaining, will, "on account of spastic phenomena," lead to the clinical manifestations of the disease during the first few weeks of life. The proponents of the theory explained the frequent spontaneous improvement of cases by stating that the hypertrophied gastric musculature may, in time, overcome the obstructive resistance of the pyloric region; they further theorize for cases that develop the symptoms weeks or even months after birth by saying that these have an incomplete degree of obstruction at birth and that the phenomena of irritation, that completes the obstruction, will occur later. The only concrete evidence in support of this theory is Holt's observation that in infants with functioning gastroenterostomy the pyloric tumor persists for years. This statement has not, however, been corroborated and later observations on cases after the Fredet-Ramstedt operation reveal complete disappearance of the tumor (Lan-

man and Mahoney and Donovan). The most damaging evidence against the theory is the fact that a typical pyloric tumor has never been found in a premature infant unless it had lived for some length of time (Lehmann and Schmid). On the grounds of the accepted teratologic principles one may also object that malformations always represent a defective rather than an overdeveloped genetic process.

Another group of authors consider the pyloric tumor to be *the result of work hypertrophy* occurring in fetal life. Dietrich and also Willi (cited by Uhr) believe that obstruction of the pylorus may be due to a shortened hepatoduodenal ligament. Others see the cause of impeded pyloric function in fetal peritonitis (Heusch, cited by Schmid); periduodenitis (Ramstedt); or anatomic abnormalities such as misplacement of the cecum or superior mesenteric artery (Schmid). The supposition of all these authors is that a functional hypertrophy takes place before birth owing to mechanical obstruction of the pyloric outlet. Thomson's assumption differs only in that he postulates a "nervous incoordination" of the pyloric and gastric musculature leading to disturbance of emptying.

The so-called *spasm theory* (Wernstedt, Bromann, and Pfaundler) regards the spasm of the pyloric musculature as the primary factor and the hypertrophy as a result of the spasm. (Pfaundler originally went so far as to deny the existence of hypertrophy, accounting for the gross appearance of the pyloric region by a "shift of muscle volume and the state of spastic contracture.") Various factors have been sought to be made responsible for the initiation of the spasm: local erosion (Ernberg), irritating foodstuff, defective development of the vegetative nervous system, birth injury of the vasomotor and vomiting centers. The chief refutation of the theory has come exactly from the futility of the attempts to demonstrate these alleged initiating factors. Clicinal investigation also failed to yield convincing evidence of neurologic disturbance of the infants affected. Moreover, the holders of this view fail to distinguish adequately between the pyloric canal and the pyloric sphincter proper, two anatomic structures of well-defined and different functions. In general, they consider the entire pyloric region as one anatomic unit. But a spasm of this region should obviously lead primarily to a hypertrophy of the wall of the body of the stomach rather than of the pyloric canal.

Because of the deficiencies of these theories, numerous ideas have been advanced to bolster or replace them.

Vollmer believes that the *alkalosis* produced by any kind of severe vomiting will bring about vagotonia and this, in turn, spasm of the pylorus.

Pirie developed the rather complex train of thought that the *hyperadrenalinemia* often noted in pregnant women causes a depression of the function of the pancreas of the fetus; this in turn leads to a hypermotility of the duodenum that interferes with the orderly opening of the

pylorus and gives rise to pylorospasm. Although Pritchard and Hillier, and Gray and Reynolds also attempted to support the role of hyperadrenalemia in the causation of the disease, the available evidence is not at all convincing.

Forssell has advanced the idea of "*disturbed autoplasticity of the pyloric mucosa.*" According to him the pyloric mucosa possesses the ability of self-regulatory movement (autoplasticity) and may act as an important agent of the closure of the pyloric opening (so-called *torus pyloricus functionalis* or "functional pyloric stopper"). The first step in the genetic events of pyloric stenosis is, states Forssell, the impairment of this autoplasticity. He conducted some very painstaking and ingenious radiographic investigations in proof of his ideas, but his work has remained unconfirmed.

Moore and his co-workers have shown that rats fed on a diet deficient in the *vitamin B complex* develop, particularly in the second generation, among other changes, a type of hypertrophic pyloric stenosis together with myelin degeneration of the vagus. By analogy they claim that the cause of infantile pyloric stenosis of the human being is the same. There have not been sufficient clinical investigations carried out to prove or disprove this statement by dietary studies, although the theory may have some merits (e.g., it suggests an explanation for the so-called racial affinity and familial incidence of the condition).

An ingenious theory has been published by Stolte. He came upon the idea that the hypertrophic pyloric musculature in the male infant is the counterpart of the hypertrophic uterus of the newborn female (which, as is well known, is as large as that of a 7-year-old girl), both being affected by the *growth-promoting hormone* circulating in the maternal blood during pregnancy and present in the maternal milk. The idea has obvious attractions: it checks with the sexual distribution of the disease and with the seeming frequency of breast feeding among the patients. It is hard to explain, however, why the pylorus should be particularly susceptible to the hormone; the prostate would be a more logical site. In addition to several other objections, one may mention that the measurements of the pyloric musculature show no appreciable differences in the normal male and female infants (Beumer and Hückel). However, the idea has never been subjected to laboratory research.

Lehmann considers the initial stages of hypertrophic pyloric stenosis *analogous with the essential features of cardiospasm*, the cause of which is the achalasia of the cardiac sphincter. According to the best current opinion, the pyloric sphincter (as distinguished from the musculature of the rest of the pyloric canal, a primarily propelling muscular mechanism) is in a state of tone when not actively working: this is the position in which it closes the pyloric outlet; its working condition comes about when it opens (Vertue, Kestner, and Rhumann). Thus the cause of hypertrophic pyloric stenosis is a congenital, hereditary inability of the pyloric sphincter to open, i.e., to perform its func-

tion. The consequence of this is a work hypertrophy of the pyloric musculature, upon which the task of overcoming the resistance of the sphincter falls. If this compensatory hypertrophy is of sufficient degree, no clinical symptoms will appear. Further, Lehmann postulates the presence of an additional, central factor. As a result of the persistent overload on the gastric musculature, a summation of stimuli takes place in the higher nervous centers and eventually the threshold of sensory stimuli will be reduced for the central and peripheral vagal mechanism. Finally, the threshold may be lowered to the point where minimal peripheral excitation will result in contraction of the gastric wall, hyperperistalsis, and vomiting. The clinical picture will thus consist of the manifestations of the sum of these two effects: first, the inability of the stomach to empty itself when the hypertrophy of the pyloric musculature no longer keeps pace with the work demanded to overcome the obstruction, and, second, the state of central vagal hyperexcitability. According to Lehmann, most forms of medical therapy attack the central factor, i.e., attempt to increase the sensory threshold by central depression. Conversely, the surgeon directs his effort to the breaking of the first link of the chain of events, by sectioning the sphincter and thus relieving the obstruction.

As all the theories opposed to the concept of congenital etiology, Lehmann's view is subject to the criticism that the short interval between birth and the appearance of the disease is an insufficient length of time for the development of a high degree of muscular hypertrophy. This objection is, however, a decidedly speculative one. Lehmann's hypothesis, on the other hand, has much supporting evidence in fact.

Recently Herbst (and others, cited by v. Mettenheim) demonstrated changes of degeneration in the axis cylinders and ganglion cells of the wall of the pyloric canal and stomach proper. Since in achalasia of the cardia (Hurst, cited by Vertue) similar pathologic changes have been reported, this observation would seem to make the analogy between achalasia of the cardia and achalasia of the pyloric sphincter, as postulated by Lehmann, even stronger. It could be further presumed that the nerve changes represent a failure of normal development, perhaps on a hereditary basis, which may, under favorable circumstances, correct itself by the third month of life, when, in fact, the symptoms of this disease usually disappear spontaneously.

The roentgenologic studies of Meuwissen and Slooff, Runström, Wallgren, Frimann-Dahl, Jochims, Andresen, and others have demonstrated that one can, with great precision, delineate a period of growth in the evolution of the pyloric changes. There have been very early cases observed with definite x-ray changes but without clinical symptoms (Wallgren). In instances of reoperation, a progress in the growth of the tumor has been repeatedly noted. Roentgenologically it has also been shown that the progress in the size of the tumor takes place as the result of the incorporation of new hypertrophied muscle fibers orad;

concomittantly the lumen becomes narrower and, as demonstrated by operative observations, the wall of the pyloric canal becomes increasingly thicker. Eventually a length of 10 to 24 mm. will be reached as compared to the normal length of 1 to 4 mm. These phenomena evidently fit into Lehmann's theory well. According to him the changes in the pyloric canal are those of work hypertrophy, thus a varying length of time will be required for their full development. Moreover, as long as the compensatory hypertrophy is adequate to its task, no symptoms will develop; thus, the asymptomatic cases with x-ray evidence of pyloric changes will be explained.

In a very comprehensive review of the problem Schmid has also formed the opinion that the pyloric swelling is the result of a true hypertrophy of the muscular wall, brought about by a persistent "state of tension" of both the longitudinal and the circular muscle fibers. Instead of a primary obstruction at the pyloric opening, such as the achalasia postulated by Lehmann, he suggests the presence of a somewhat mysterious "stimulus" that initiates the condition of increased tension in the muscular elements. He believes that he has found proof to identify this initiating factor with *hereditary allergy*. (In this connection it may be noted that Balyeat and Pounders, Cohen and Breitbart, and Rowe have also called attention to the possible role of allergy in the etiology of infantile pyloric stenosis.)

Of particular interest is Schmid's explanation of the strikingly uniform anatomic configuration of the pyloric tumor. Although puzzling even at first sight, the strict limitation of the muscular hypertrophy to the boundaries of the pyloric canal had not been quite satisfactorily clarified before. From considerations too lengthy to be repeated Schmid concludes that the upper limit of the extent of the tumor is determined by the anatomic disposition of the hypertrophic muscle fibers that causes them to lose their mechanical efficiency above the angle of the pyloric antrum. (It is generally agreed that the sphincter is spared of the process of hypertrophy because it is a structure apart from the pyloric canal.)

Summary of the Theories and Facts of Etiology.—There is no valid evidence to sustain the view that the pyloric tumor of infantile pyloric stenosis is a malformation or, in other words, a birth anomaly. Its pathologic features, its symptomatology and its response to treatment prove this lesion to be a form of quasi-physiologic tissue reaction, most likely a type of work hypertrophy, in response to some abnormal stimulus. Two fundamental questions remain to be answered. First, does the development of the pyloric tumor always occur postnatally? The best answer to this question is a qualified "yes"; while in the great majority of cases the lesion evidently develops after birth, in a few cases one must assume that at least the earlier phases of the pyloric swelling must have had their origin in utero, i.e., during the last days of intrauterine life. It must be added that this possibility does not

necessarily refute the supposition that the pyloric changes are those of a type of work hypertrophy rather than of malformation. The other problem concerns the nature of the stimulus that calls forth the series of events leading to the pyloric tumor. The identity of this stimulus is not definitely known, although a number of factors, such as factors of race and sex, the high incidence in the first born, and a strong hereditary factor, have been recognized that must have some hitherto unexplained relationship to it.

The theory that binds the known facts and assumed possibilities into the most plausible sequence of events is that of Lehmann. For the time being this must be considered the most logical hypothesis of etiology even though it, too, overlooks the effects of some important factors of pathogenesis (race and sex incidence, frequency in the first born) and leaves unsatisfactorily explained some commonly seen phenomena (early postnatal appearance of pyloric tumor). The steps in the structural evolution of the pyloric tumor have been best elucidated by Schmid.

SYMPTOMATOLOGY

Incidence.—No reliable data of incidence are found in the literature. According to Hertz (cited by McGill) 2.7 per cent of all infants below 1 year of age show the disease, but this seems altogether too high a figure. At the Henry Ford Hospital about 3 to 4 of every 1000 infants less than 1 year old have had the disease. Since about 1925, a marked increase in the number of reported cases has been noted, unquestionably due to the more frequent clinical recognition of the disease.

Vomiting.—At birth the child tends to be particularly lusty and well developed. The average birth weight has been recorded in the various series as about 3500 Gm. for boys and about 3000 Gm. for girls (Faxen, Mouriquand, Rinvik, Svensgaard, Strauss, Wallace and Wevill). The first days of life are also, as a rule, normal. During the third or fourth weeks of life, however, the infant begins to vomit its feedings. The vomiting first follows the intake of food by some minutes, and there may even be some meals retained. Gradually it becomes more severe and it soon reaches a point where it starts with the first gulps of food. According to the reports in the literature the most common time of the onset of vomiting is between the second and sixth weeks of life, with the peak during the third and fourth weeks (Behrmann, McGahee, Monrad, Rinvik, Salmi, Still, Strauss, Svensgaard, and Wolff) during which nearly one-half of all cases occur. Seventy to eighty per cent of the cases will appear during the first six weeks of life. The average age at the onset varies between 21 (Brown) and 28.5 days (Rinvik). The first symptoms have been observed to show in some cases as late as four, six, or even nine months, but such cases are very rare. In fact, for all practical intents the statement appears to be true that after the second, at most the third, month of life the disease is not seen (Ramstedt and v. Mettenheim). About 10 per cent of the cases start at birth.

In our material, 80 per cent made their appearance during the first four weeks of life (exclusive of three cases on which we have incomplete information).

An important characteristic of the vomitus is its freedom from bile or other duodenal contents. As a rule it does not contain blood. Only Svensgaard and Rosenbaum report important incidences of bloody vomitus (36.7 per cent and 23 per cent respectively). Ernberg finds it frequently, but gives no figure. Frank hematemesis has never been observed (Rinvik). In our series blood was noted in the vomitus once; in three instances the necessary information was not given.

In other respects an analysis of the returned stomach content yields nothing characteristic. The acidity is usually increased owing to the presence of decomposition products. In advanced cases hypochlorhydria and hypoacidity are found.

The vomiting often starts as a simple regurgitation but practically always becomes forceful and projectile in type. Projectile vomiting must be considered as the sine qua non of the diagnosis of infantile pyloric stenosis. It has been found present in virtually every case; even when not decidedly forceful, the vomiting is of such severity that it is only a matter of personal estimate whether one labels it projectile or merely "vomiting." Among all our cases the type of vomiting was thought to be projectile except in one instance, but in this it was extremely persistent and associated with visible peristaltic waves. (In one instance the type of vomiting was not stated.) It is characteristic of the vomiting that it is entirely refractory to the usual therapeutic measures of modification in the feeding formula, and that it is unaccompanied by manifestations of a febrile disease.

It should be noted briefly that vomiting may be entirely absent in spite of the presence of the typical pathologic changes in the pylorus (Bexelius, Findlay, Wallgren, and others). This phenomenon will be easily understood in light of the modern concept of pathogenesis of the disease (vide supra), and, for obvious reasons, has no bearing on the practical diagnostic importance of the symptom of vomiting.

Usually after an attempted feeding, but often independently of it, *waves of gastric contraction* can be seen passing across the child's upper abdomen from left to right. This sign, too, has been observed in almost every case reported and is the second cardinal point of diagnosis. But it is not pathognomonic; peristaltic waves of the same description have been noted in a variety of conditions other than pyloric stenosis (Gardère and Viallier, Mouriquand and Weill, Holt, Still). In our own material this sign was observed in 81 per cent of the cases.

In a number of cases the *pyloric tumor* can be palpated, usually in the right upper quadrant, high under the costal margin. The proportion of cases in which the pyloric thickening is reported to have been palpable varies quite widely: Bodley, 5 per cent; Brown, 54 per cent, Donovan, 100 per cent; Lanman and Mahoney, 98 per cent; Lereboullet, 66 per cent; McLeod, 84 per cent; Meredith, 87 per cent; Still, 100 per

cent; Strauss, 25 per cent; Wallace and Wevill, 24.1 per cent; Wyatt, 33.3 per cent; Svensgaard, 87 per cent. Fredet can palpate it only "rarely" and Strachauer "very rarely." According to Ramstedt the palpation, for anatomic reasons, is possible only in very lean subjects: ordinarily the pylorus is located near the spine, behind the liver and under the cover of the antrum and stomach. Moreover, it has been claimed that the pyloric tumor changes its consistency from time to time (Ibrahim and Wernstedt); others deny the presence of this phenomenon (Heile and Ramstedt), but if it should exist, it could further increase the difficulties of palpation. There has been a great deal of discussion about the question of whether or not the palpation of the pyloric tumor is a requisite of diagnosis. Since the success in demonstrating this sign depends upon so many subjective factors one cannot insist on its presence for a positive diagnosis. When it is present, however, its significance is virtually pathognomonic. In the literature, instances in which a pyloric tumor was with certainty felt before, and found absent during, operation are quite rare (Downes and Ramstedt). It is, furthermore, evident that with increased experience and with a great deal of patience, the successes in palpating the tumor can be raised to about 80 or 90 per cent. Since a positive assurance that the tumor is present makes further investigations dispensable, one should attempt to demonstrate it, by all means. The diagnosis, however, can be ascertained by other methods, should one be unable to do so. We have been able to demonstrate the thickening of the pylorus in 56.0 per cent of the cases.

On account of the persistent vomiting, after a varying length of time, profound *metabolic changes* appear in the infant's organism. The most conspicuous of these is the *reduction of the volume of feces and urine*, frequently noted by the parents themselves. The scantiness of feces, which are greasy and consist mainly of bile, pancreatic juice, mucus and epithelium, is, of course, due to the lack of food entering the intestinal tract and is commonly taken for constipation, a symptom reported by the mother in about 90 per cent of the cases. In a small proportion of cases (Uhr) a spurious, "hunger" diarrhea may develop caused either by profuse intestinal mucosal secretions or by the mother's attempts to overcome the apparent constipation. The oliguria is merely another expression of the dehydration which is manifest in the entire appearance of the baby.

The most important metabolic changes take place in the *blood chemistry*. The extensive studies of Schnohr, Seckel, Maizels, and others have demonstrated that the continuance of the vomiting as the disease progresses leads to a severe chloropenia (serum NaCl 350 mg. per cent or less, Seckel) and that this, in turn, gives rise to alkalosis, azotemia, and hyposmosis. The hypochloremia may be of such degree that it brings about chloride depletion of the tissues (Schnohr). A state of disturbed consciousness will eventually ensue, the so-called pyloric coma, characterized—in addition to a mental stupor—by shallow breathing,

muscular hypertonia, and nontetanic convulsions. Findlay has expressed the view that the fall of chlorides in the urine cannot be strictly correlated with the severity and duration of vomiting and that, in some way, perhaps by the action of a toxin, the chlorides become fixed in the tissues. No corroboration of this contention has come forth from other quarters. On the contrary, it is generally held that the blood chemical changes can be taken as an index of the severity of the disease and thus they are of great prognostic value. They would deserve more practical clinical application than hitherto allotted.

In addition to hypochloruria albuminuria, acetonuria and glycosuria have at times been noted (v. Mettenheim).

In our material, unfortunately, the blood chemical studies have been so sporadic as to preclude any conclusions. The common laboratory methods (urinalysis and blood counts) routinely used on our service yielded no distinctive diagnostic information.

The final important consequence of vomiting, and usually the first one to cause sufficient alarm to suggest the necessity of a medical consultation, is the cessation of the normal gain in weight and, eventually, a *loss of weight*. Since one seldom has an accurate idea of the rate of gain of the infant prior to the onset of the disease, it is customary to compare the weight at admission to the birth weight in order to make an estimation of the magnitude of loss. This varies widely, but in a large proportion of the cases the admission weight will have fallen under the birth weight; e.g., this was the finding in 57 per cent of Tallerman's patients. Strauss records the average loss from birth weight as 240 to 450 Gm., while Svensgaard's figures are 100 to 280 Gm. The general impression is that the weight losses observed in more recent times are less than those of former years, although accurate comparable figures are not available. Among our patients the average birth weight was 3535 Gm., the average admission weight 3597 Gm.

In advanced instances of undernutrition the dehydrated, wasted infant, with its collapsed lower abdomen and prominent, tense epigastrium, makes a striking and sad picture. In patients in poor general condition the temperature is usually subnormal. At times, however, temperature elevation may be present, generally ascribed to the disturbance of the temperature-regulating cerebral center (v. Mettenheim).

Differential Diagnosis.—It is usually a simple matter to eliminate the possibility of infectious vomiting on grounds of the absence of high fever, dyspeptic stools, and an acute infectious disease. In the presence of the typical findings just discussed (persistent, projectile vomiting, epigastric peristaltic waves, loss of weight, and palpable pyloric tumor, to which may be added the typical blood chemical changes and the presence of constipation), there are few organic diseases of the abdomen that may lead to confusion in diagnosis (Hipsley). The rare congenital anomalies of the pylorus and peripyloric region (vide supra) will, as a rule, be mistaken for true hypertrophic stenosis, but such mistakes

will result in no harm if surgical treatment is resorted to as indicated by the standard operative criteria. The same is true of the obstructive lesions of the duodenum (Ladd and Burt and Tyson). Moreover, these duodenal diseases frequently may be differentiated by the presence of bile in the vomitus, and almost invariably by means of radiographic studies. Yet there will be cases where only surgical exploration will yield the diagnosis (Burt and Tyson).

It is not these lesions that create the commonest diagnostic problem but the symptom complex called pylorospasm. By definition, pylorospasm is a form of pyloric obstruction due to a purely neurogenic dysfunction (presumably spasm) of the pyloric musculature. The diagnostic criteria of this condition have not been very clearly stated but they appear to be (Shanley): a transitory character of the obstruction, a less violent, less persistent and usually nonprojectile character of the vomiting, less preponderance of involvement in the male, later onset and, in general, a less malignant course.

About the relationship of this syndrome to organic pyloric stenosis the opinions are either sharply divided or noncommittally vague, Holt claims that this condition exists only as a transitory state, wholly incapable of giving rise to a disease picture of importance. According to his view the vast majority of the instances labelled pylorospasm are mild forms of organic pyloric stenosis. Mitchell supports this view, and Ramstedt and Halbertsma admit that true pylorospasm is very rare. On the other hand Higgins, Tallerman, Tisdall and others agree that a sharp distinction should be made between the two conditions. In general the French, British, and a part of the American authors incline to a differentiation of the two disease pictures, whereas in the German literature the distinction is much less marked.

From this controversy one gains the impression that the disagreement springs from an exaggerated and unnecessary delimitation of diagnostic criteria. But for the absence of a palpable pyloric tumor, the signs and symptoms of pylorospasm reveal no essential qualitative difference from those of organic pyloric stenosis; the distinction is merely one of degree. It has been already shown, however, that the presence of the pyloric tumor is ofen difficult to establish and that, therefore, it cannot be considered an indispensable diagnostic sign. The hitherto puzzling phenomenon of the absence at operation of a pyloric tumor in spite of the presence of all the other cardinal signs and symptoms of pyloric stenosis—a phenomenon considered the strongest evidence in favor of the separate existence of pylorospasm—can be explained logically in terms of the modern concept of pathogenesis of pyloric stenosis; one no doubt deals, in these cases, with early examples of the disease, when the process of hypertrophy has reached only a mild degree, or else the hypertrophic changes have already begun to regress. Thus, the conclusion is inescapable that if one views the diagnostic criteria comprehensively, the differences between the two

conditions are so slight as to make the segregation of pylorospasm as a disease sui generis unwarranted. On the contrary, it seems likely that this symptom complex is merely a milder, more benign form of the organic stenosis. In fact, progression of this form into a more severe form with all the characteristics of organic pyloric stenosis has been observed (Uhr). Further, it seems probable that there are cases of transient vomiting caused by temporary pylorospasm, in the meaning of Holt, but by no means deserving classification as a disease entity. The differentiation between pylorospasm and pyloric stenosis is, therefore, unnecessary from the pathologic point of view; it may, however, be well to remember the distinction between the two types of disease state from the therapeutic point of view since the benign form will do well on medical management (vide infra).

Roentgenologic Characteristics.—The roentgenologist's main diagnostic problem has been the differentiation between pyloric stenosis and pylorospasm, or more precisely, the decision as to whether the case in question was a surgical or a medical responsibility. The conventional radiographic criteria (Lereboullet, Mouriquand, Viethen, Contamin) have for some time been the dilatation and general atony of the stomach with intermittent hyperperistalsis and a great delay in emptying. In contrast, in pylorospasm the stomach is found to be normal in size, hypertonic, and of more nearly normal emptying time or with an all-or-none evacuation. Obviously, these differences are to be regarded as the different phases of the same process. As the modern etiologic concept sees it, the first group of changes represents a viscus that has undergone a series of compensatory changes and is now failing in function; it is an advanced phase of the process. The other series of appearances are characteristic of the stomach in the early phase; there is evidence of obstruction but with full compensation at work. As additional evidence to the operative indications, these criteria are very helpful, as shown by Calvin and Denenholz, who, by the evidence of 60 to 100 per cent three-hour retention, were able to diagnose the presence of pyloric stenosis in every one of 96 cases. Of the 20 cases we have studied radiographically, 18 showed a three-hour retention of 75 per cent or more; in 16 cases the retention was 90 per cent or more. Of particular interest was a case in which the three-hour retention was 35 per cent, or nearly normal; this case was a typical picture of surgical pyloric stenosis and at operation displayed a well-developed pyloric tumor. It is to be noted further that in three instances, normal, and in one instance, increased, tonicity was found, and that three stomachs showed no increase in size. Nevertheless, all these viscera presented characteristic surgical findings.

Similar failures of the conventional radiographic signs, though relatively few, have been observed by others (Shanley). Andresen, Frimann-Dahl, Jochims, Meuwissen and Slooff, Runström, and others have

demonstrated that the emptying time is of secondary importance. Their findings may be summarized as follows:

Under the fluoroscope no peristalsis can be seen in the region of the pyloric canal. The stomach shadow comes to a sudden end at the pylorus. At times a widening of the prepyloric segment to the right and downward is evident, so that the greater curvature descends to the antrum abruptly and vertically. In regular intervals, deep peristaltic waves are noted as if caused by the sudden relaxation of the gastric musculature. The contrast medium must be gently pressed into the pyloric region; then it is possible to demonstrate the stringlike, narrow, and elongated pyloric canal. Roentgenograms should be taken in an oblique diameter with the patient prone. The unfailingly typical roentgen evidence of the disease is afforded by the appearance of the pyloric canal which is four to five times its normal length and only a millimeter or two in width.

Whereas few critical voices have been raised against the accuracy of roentgen diagnosis (Findlay and Shanley), the opinions concerning the advisability of the practical application of radiographic methods are sharply divided. Heile, Lereboullet, Mouriquand and Weill, Rinvik, Rohmer, and Strauss use roentgenologic examinations almost routinely and find them very useful or even indispensable. But Brown, Donovan, Ladd, Robertson, and Wyatt consider these examinations superfluous and even harmful. The usefulness of the method undoubtedly depends on many local factors. Where surgical treatment is routine, for instance, the x-ray investigation will be unnecessary for completing the operative indications; one will operate in any case. On the other hand, if one tries to select the operative cases with the greatest care, and with the help of all available means of information, the radiogram will be of decided assistance. The alleged harm that may come from the ingestion of the barium meal is probably imaginary; it has never been actually observed. We have found the roentgenologic studies helpful in nearly every case, indispensable in a few, deleterious in none.

TREATMENT

Medical.—The earliest modes of treatment of infantile pyloric stenosis were of course medical: frequent small feedings, modification of milk mixtures and milk substitutes, and lavage of the stomach in order to get rid of the decomposing foodstuff stagnant in the stomach. At times the early dietary measures appear astounding, even if not lacking in ingenuity. Fabricius Hildanus, for instance, ordered "meat-juice with olive oil" in place of the habitual "corn-pap." (It was a wise change, though, for this the first known victim of infantile pyloric stenosis made a nice recovery.)

No fundamentally new therapeutic idea appeared until the latter part of the nineteenth century when Heubner introduced the use of hypnotics on the theory that the alleged cause, the spasm, would thereby

by relieved; tinctura opii and various papaverine compounds became the most popular of these.

Apparently it was Strümpel who, in 1904, first tried out and advocated atropine (in the form of tincture of belladonna) for the relief of the spasm that was the generally accepted etiologic factor. This drug made slow headway in popularity and became widely used only after the 1920's.

In 1914, Birk described the beneficial effect of corn-meal mush as a substitute for liquids in the infant's diet. Independently, Sauer, in this country, called attention to the usefulness of farina paste, at about the same time. The rationale behind these attempts to feed food of thick consistency was that thus a stimulus is supplied for the deficient peristolic function (gripping force) of the stomach (Rogatz). "Thick feeding" with the administration of atropine and juggling of the feeding schedule and milk modifications has become the standard conservative means of treatment in this country. The same plan with different substances is used elsewhere in the world. Gastric lavage is still practiced by some but, in view of the better understanding of the blood chemical changes, it is discouraged, since it tends to aggravate chloride depletion.

The most important innovation in the drug therapy of the disease in almost forty years was the application to internal treatment of the drug eumydrine by Drucker and Usener of Copenhagen (1926). This methylnitrate derivative of atropine was originally proposed for use as a mydriatic (hence its name), but later it was found that it had the full internal action of atropine with only one-fiftieth of its toxicity. With its use remarkable results have been obtained.

Here the pharmacologic properties of atropine (and eumydrine) and its possible mode of action in infantile pyloric stenosis may be briefly considered (McSwiney and Vertue). The pyloric sphincter is normally closed. When a wave of contraction starts in the pyloric antrum the sphincter relaxes and remains open for five to six seconds. About a second before the wave reaches its summit the sphincter closes again and stays closed during the remainder of this wave and afterwards until the next. These movements are governed by the intrinsic nervous system. The opening and closing can be influenced by local events (acidity and osmotic pressure of the gastric contents, and intraduodenal pressure). The stomach has a double nerve supply: sympathetic and vagal; the mechanism thereby governed is rather complex. Section of the vagi causes diminished tone, slow peristalsis, and delayed emptying. Stimulation of the vagi usually causes dilatation of the pyloric sphincter and increase in the tone and movement of the stomach; but if the stomach is already in a state of high tonus, the effect is the opposite. Stimulation of the splanchnics causes the body to relax and the sphincter usually to contract; but if the sphincter is already hypertonic, it relaxes. The net result depends not only upon which nerve is stimulated but also upon the condition of the stomach at the moment. Atropine has

a general paralytic effect on nerve endings in the stomach. Given intravenously to cats, it causes a general relaxation of the stomach, a fall in intragastric pressure, and an arrest of movements. If one now presumes that the primary difficulty in infantile pyloric stenosis is the spasm of the sphincter, then medicinal doses of atropine (or eumydrine) must be blocking impulses to the sphincter without inhibiting peristalsis—a highly complex and difficult goal to attain. But if it be supposed to be an achalasia, the explanation is much simpler; the general relaxation in which the sphincter shares is reached before peristalsis is abolished.

It may be added that the central depressant action of atropine may be of more therapeutic importance than is generally appreciated (Lehmann).

There have been a number of other drugs employed in the treatment of infantile pyloric stenosis but none achieved any popularity: subcutaneous suprarenin, scopolamine, and hyoscine mixtures (so-called vasano), papaverine (Bókay) in combination with eumydrine, and a whole series of hypnotics. The application of the latter group was by some developed into the so-called twilight-sleep therapy, during which the child may be kept unconscious for a number of days or even weeks. The central idea in the rationale of the use of cerebral depressants is the recognition of the fact that these infants present a high degree of nervous excitability, as propounded in Lehmann's theory of pathogenesis. The presence of gastric hyperperistalsis caused by many superficial stimuli other than ingestion of food is one of the manifestations of this state. Moreover, the extent and intensity of vomiting of these children are not direct functions of the degree of pyloric obstruction; as Ramstedt has pointed out, in obstructing pyloric ulcer of the adult even the highest grade of obstruction will fail to lead to a picture similar to the protracted vomiting and excessive gastromotor irritability that are commonly observed in the stenotic infant. (See also Haverschmidt and Bókay.)

As curiosities one may mention the methods of treatment with x-ray irradiation (Wiener), diathermy (Tobler) and foreign-protein injections (v. Mettenheim).

In the early 1920's, Gerstley called attention to the period of relative cessation of irritability immediately after a spell of vomiting. He advocated, therefore, refeeding of small amounts of food ten to fifteen minutes following the last attack. The method appeared to have merits in selected instances.

Particular stress should be laid on the importance of subcutaneous and intravenous fluid therapy (including blood transfusions), which became widely used only in the early 1920's, and, together with the improved hygienic conditions of the infants' ward and the refinement of infant nursing care, has been the all-important factor in the production of the low mortality rates of the latter years.

Surgical.—History: The development of the surgical treatment of infantile pyloric stenosis lagged a few paces behind the general advance of surgery, perhaps because it required an extra measure of fortitude to put the knife to the feeble infant body. And since, as the most obvious line of attack, the early operators attempted to apply to the problems of the infant technical procedures devised for adults, the decision of making the trial had to wait until the value of the method had been established and the difficulties of technique overcome. Even thereafter the progress was slow. The story of the surgical therapy of infantile pyloric stenosis is a fitting illustration of the old truth that discoveries are seldom achieved by bold leaps but rather by short and faltering steps that as often slide back as stride forward but always tread the path smoother for those coming behind.

The first operation ever performed for the disease certainly cannot be regarded a step forward. Cordua of Hamburg, Germany, in 1892, performed a jejunostomy on a male infant sick with pyloric stenosis. The outcome was fatal. This type of operation was never again recorded in the literature.

The next operative intervention, and at the same time the first one in the United States, was that of Willy Meyer who, in 1897, performed a posterior gastroenterostomy with Murphy button.* A few weeks later Stern of Germany did an anterior gastroenterostomy. Both these cases ended fatally shortly after the operation.

The credit for the first successful operation of any type must go to Löbker, a German, who in 1898 obtained complete cure with a posterior gastroenterostomy. During the subsequent fifteen years gastroenterostomy, anterior in more severe cases, posterior if the patient's condition permitted it, became the most popular procedure.† From 1897 till 1908, it was performed fifty-two times with a mortality of 59.6 per cent (Abel, Dufour and Frédet).

In the latter part of the nineteenth century the so-called "pyloric divulsion" of Loretta was a commonly employed operation for various types of pyloric stenosis in the adult. The main steps in its technique were the opening of the stomach and the introduction of a mechanical dilator with which, then, the constricted pyloric canal was forcibly enlarged. With the advent of pyloroplasty the procedure fell into disrepute, but Nicoll of Glasgow applied it with some success to the treatment of infantile pyloric stenosis. Altogether, thirty-six such interventions were reported by him and others until 1908, with an over-all mortality of 41.1 per cent. Nicoll later added a gastroenterostomy to

*Gastroenterostomy was first attempted by Wölfler in 1881; this was an anterior operation; the first posterior gastrointestinal anastomosis was performed by v. Hacker in 1889.

†It is of more than passing interest to record that among the fairly large number of gastroenterostomies performed in infants only one reported case of marginal ulcer has been found; this ulcer occurred in a 9-month-old baby and was fatal (Kausch).

the divulsion, and his mortality with this combined operation (seven cases) was around 30.0 per cent. In 1906, he published the description of a so-called V-Y pyloroplasty in conjunction with the divulsion; he lost only one of the six cases in which he used this technique. It is worthy of note that in his report he, rather vaguely, mentions that under some circumstances (he failed to mention under what circumstances) the pyloroplasty must be made without opening the mucosa.

Nicoll's creditable results were not duplicated by others using the same method. The combined mortality rate in 113 cases in which all the methods so far mentioned were employed (reported up to 1908) was 50.5 per cent. It was generally recognized that a good share of the responsibility for the high mortality had to be ascribed to the technical difficulties of the procedures. To simplify the intervention, Braun, in 1900, introduced the use of the then rather new Heineke-Mikulicz pyloroplasty (first performed in 1887) for infantile pyloric stenosis. The technique attained some measure of popularity and its results were slightly better than those of the older methods.

As used in the infant, however, pyloroplasty had decided disadvantages. While generally recognized, these objectionable qualities were first critically analyzed by Frédet. He wrote (in 1908): "Cette manière de faire n'est pas, il faut l'avouer, sans inconvenients. Elle oblige à ouvrir une cavité septique, à sectionner la muqueuse qui saigne. Il est malaisé d' assurer l'hémostase en faisant la suture de la muqueuse, difficile également d'obtenir une suture parfaitement étanche." Frédet undertook to eliminate the first two technical imperfections of the procedure (the opening of an infected cavity and the sectioning of the vascular mucosa with its danger of hemorrhage) by carrying his longitudinal incision only as far as the submucosa, leaving the stomach unopened. He then proceeded to suture the muscularis transversely, in the standard manner. His first operation was performed on Oct. 12, 1907.

It invites speculation to note that he had in his grasp the solution of the third technical problem, the difficulty of closure of the hypertrophic muscle wall, but somehow he did not realize it. He describes in detail his inability to place accurate sutures into the muscle layers of the pylorus; the excessive tension would tear the thread out. He was even obliged to leave a diamond-shaped area of submucosa uncovered by muscle. Although in this case recovery was satisfactory, the idea of overcoming the difficulties of cross-suturing, required in the Heineke-Mikulicz pyloroplasty, by omitting the sutures was apparently too revolutionary to enter his mind.

Frédet's experiment was exactly duplicated by W. Weber in Germany. Weber, who was unaware of the work of Frédet, nevertheless evolved the same technique, and on Dec. 3, 1908, performed it with success. Of his next two cases thus treated, however, one died of hemorrhage.

This and Kausch's severe criticism of the procedure, which followed Weber's publication by a few days, were important factors in dampening the interest in the new operation. Kausch, then one of the high priests of German surgery, condemned the method in strong words, claiming that the cross suturing, far from increasing the lumen of the pylorus, will aggravate the obstruction by folding the mucosal lining into creases. At any rate, the operation was not again reported upon until 1912, when Ramstedt* revived it with the addition of his own modification.

He first performed it in September, 1911, following Weber's technique step by step. (Frédet's previous article was unknown to him, too.) He was impressed by the ease with which the edges of the wound in the muscular wall of the pylorus gaped and the submucosa bulged. The patient continued to vomit for a few days and in general had a hard time. Then suddenly the vomiting ceased and thereafter the infant made an excellent recovery. Ramstedt remembered Kausch's warning about the cross suturing of the thick muscle layer; he also recalled that the edges of the wound could be closed only under a great deal of tension. The sudden turn in the postoperative course could be explained in but one way, he thought: the sutures gave way, the wound righted its direction, allowing the edges to separate and the mucosa to protrude, as they had a tendency to do, and thus the obstruction was overcome. In the future the operation should be carried out in this, the only physiologic way, he concluded. On Jan. 18, 1912, he had an occasion to try this idea, and the patient in this case recovered smoothly. In the same year he reported his two operative cases, setting forth very clearly the rationale of his method and advocating it as the technique best suited to deal with the problem of infantile pyloric stenosis.

There is little doubt that the popularity of the submucous operation takes its origin from Ramstedt's first publication. Even for some time after this article had appeared, Frédet's and Weber's work remained forgotten. It is only fair to remember this when one assigns credit for the invention of this operative technique. It is true that like so many other scientific discoveries, it was the product of an unwitting cooperation among at least three men,† but the greatest share of recognition still must go to Ramstedt. It is undeniable, for instance, that in his original paper Frédet is vague about the operative indications of his submucous pyloroplasty; he himself continued to use gastroenterostomy as the method of choice until 1921; for thirteen years after its first

*In the English language medical literature there is some confusion concerning the correct spelling of this name. With the exception of his first publication, all Ramstedt's papers contain his name spelled with one "m." The "Minerva" (Jahrbuch der gelehrten Welt) (1930) also gives it with a single "m."

†If one keeps looking, one finds earlier and earlier seeds of the later thought. According to Kausch, in Mikulicz's Clinic a submucous pyloroplasty was in use years before Frédet had any conception of it. (It was so bad they never published it, he says.) Nicoll appears to have employed some sort of submucous operation, although his statement with regard to this is vague. And finally, Weber seems to have got his inspiration from Rietschel.

description he did not use the submucous pyloroplasty at all! In fact, it appears well established that Frédet took up the operation again on the spur of the growing popularity of Ramstedt's procedure, as if relearning it from the German. And Weber's work, as already mentioned, remained in complete obscurity.

Some importance is lent to all this argument about priority of credit by the question of the designation of the operation. Ramstedt advocates the use of the term pyloromyotomy, an excellent suggestion. But in general it is the name of "Ramstedt's operation" that has become accepted, save in France where Frédet gets all the credit and Ramstedt is unknown. If one holds to the questionable habit of eponyms, Frédet-Ramstedt or Frédet-Weber-Ramstedt would seem to be the fair designation to use.

In the United States the beginning of surgical therapy of infantile pyloric stenosis was marked by the unsuccessful attempt of Willy Meyer, already quoted. To Elting belongs the credit for the first surgical cure of the disease in this country (1904). In the subsequent years the excellent work of Scudder, Richter, and Downes made gastroenterostomy the most commonly used procedure. These three surgeons had a combined mortality rate of slightly over 20 per cent (Downes), a very good record at the time. The introduction of the Frédet-Ramstedt technique by Downes (April, 1914)—first in conjunction with pyloric divulsion, then in the classical form—marked the advent of a new era, in which American surgeons (particularly Donovan, Ladd, and Strauss) attained unsurpassed results.

Surgical Versus Medical Treatment.—Before the introduction of the Frédet-Ramstedt operation the surgical therapy of infantile pyloric stenosis was an *ultima ratio physicorum,* much as primary surgical intervention for bleeding peptic ulcer is today (Bauer). If everything else failed the surgeon was given a last chance to save the infant. Gradually the situation changed, and at present the topic of discussion concerns mainly the limits of the right of the surgeon to intervene. Both for this reason and because an occasional voice is still raised in condemnation of surgical treatment it seems desirable to review the respective merits of the surgical and medical methods of therapy.

In such evaluations in the past, mortality statistics have frequently been resorted too. Raw mortality statistics should be be treated with great precaution in any case, and particular care is necessary in the case of infantile pyloric stenosis. There are inherent and almost inevitable factors in the medical and surgical series that tend to color the conclusions seriously. In clinics using both medical and surgical therapy (and these are in an overwhelming majority), the more severe cases will naturally fall to the lot of the surgeon. Thus the surgeon's mortality rate will have a heavy initial handicap. This factor of difference is only partly eliminated by the comparison of statistics from institutions using either exclusively medical or exclusively surgical

TABLE I

MORTALITY IN SURGICALLY TREATED CASES (FRÉDET-WEBER-RAMSTEDT OPERATION)

AUTHOR'S NAME	COUNTRY	YR. OF PUBLICATION	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
Still	England	1923	29	11	37.9
Bolling[1, 5]	U. S. A.	1925	454	68	15.0
Strachauer[1, 5]	U. S. A.	1927	48	1	2.1
Barrinton-Ward	England	1928	79	2	2.5
Clopton[2, 5]	U. S. A.	1928	81	10	12.4
Heile	Germany	1930	100	3	3.0
Kohl	Germany	1931	63	5	7.6
McLeod	England	1931	13	3	23.0
Page[1, 6]	England	1931	150	15	10.0
Schönbauer	Austria	1931	17	1	5.8
Hakki-Leriche	France	1932	20	3	15.0
Paas	Germany	1932	41	2	5.0
Lanman[1, 5]	U. S. A.	1933	425	27	6.3
Munting	Germany	1933	58	7	12.0
Nissen	Germany	1933	50	4	8.0
Wiedhopf	Germany	1933	15	2	12.5
Oehler[2, 5]	Germany	1934	42	6	14.0
Ramstedt[1]	Germany	1934	65	2	3.0
Spamer[4, 6]	Germany	1934	27	0	0.0
Wallace[2, 5]	Scotland	1934	145	36	24.8
Decker	Switzerland	1935	10	0	0.0
Kehl[3, 6]	Germany	1935	51	2	3.9
Rohmer	France	1935	34	4	11.4
Thompson[1, 5]	England	1935	209	30	14.4
Vanden Berg[2]	U. S. A.	1935	34	1	2.9
Bodley[2, 5]	U. S. A.	1936	60	1	1.6
Meader[2]	U. S. A.	1936	45	10	22.0
v. Haberer[1, 3]	Germany	1937	112	8	7.1
Frédet	France	1937	54	2	3.7
Kirschner[2, 6]	Germany	1937	89	5	5.6
McGahee	U. S. A.	1937	114	13	11.4
Raisch[2, 5]	Germany	1937	33	1	3.0
Salmi	Finland	1937	26	8	29.9
Strauss[1, 9]	U. S. A.	1937	431	9	2.0
Wamsteker	Germany	1937	36	0	0.0
Brown[1]	U. S. A.	1938	41	0	0.0
Lereboullet	France	1938	49	1	2.0
Mouriquand	France	1938	32	3	9.4
Pouyanne[2, 7]	France	1938	35	1	2.9
Tallerman	England	1938	98	14	14.3
Bodart[6]	France	1939	34	3	8.5
Wyatt	U. S. A.	1939	100	3	3.0
Dijkhuizen	Germany	1939	130	7	5.4
Donovan[1, 5, 8]	U. S. A.	1940	410	1	0.3
Griep	Netherlands	1940	28	1	3.4
Ladd[1, 5]	U. S. A.	1940	340	9	2.7
*Meredith[1, 5]	U. S. A.	1940	137	9	6.5
Rinvik	Norway	1940	65	4	7.6
Robertson[1, 3, 7]	Canada	1940	402	52	12.9
Shanley[1]	Ireland	1940	22	3	13.6
Williams	England	1941	70	10	14.0
Levi[1, 6]	England	1941	146	5	3.4
Total			5,399	428	7.9

*Incision: Right rectus with transverse opening of posterior rectus sheath.

[1]Anesthesia, ether.
[2]Anesthesia, local.
[3]Anesthesia, chloroform.
[4]Anesthesia, none.
[5]Incision, right rectus.
[6]Midline.
[7]Right subcostal.
[8]310 consecutive cases without death.
[9]167 consecutive cases without death.

methods, since the number of cases obtainable from such sources is quite small.

This leads to the next source of error: the set of diagnostic criteria employed. Whether or not one uses the term pylorospasm, one has ample evidence that there are mild forms of pyloric obstruction that do well on any careful conservative management. These cases, as mentioned, seldom figure in surgical statistics. The diagnostic criteria of many medical reports, on the other hand, are so loose that it seems to be a certainty that a considerable proportion of the reported cases treated conservatively do not represent, for practical purposes, the same disease that most of the surgeons are called upon to treat.* For instance, Ernberg, Monrad, and Svensgaard do not consider the presence of a palpable pyloric tumor or the x-ray appearance of the stomach at all important in making their diagnosis. Moreover, medical authors frequently exclude from their computations cases that they arbitrarily consider "hopeless" or dead of "causes other than pyloric stenosis." The surgeon has to include among his failures every case that fails to leave the hospital cured, although a considerable proportion of his fatalities are nonsurgical (see Table VI). There have even been medical statistics computed on the end results after subtraction of those cases that had to be operated upon because of failure of the medical treatment.

With all these restricting factors in mind, what can one learn from the statistics of mortality?

In Table I there are listed the end results as to survival of patients treated with the Frédet-Weber-Ramstedt operation, or one of its modifications, published in the more important reports since 1920. Cases described before 1920 were not incorporated in this compilation since either they were negligible in number or they have been included in later reports. Similar criteria were used in choosing the medically treated cases for Table II.

It is evident that both excellent and poor results have been obtained with either method of therapy, the mortality rates varying within fairly wide margins not only from country to country and from period to period but also from author to author in the same time period and geographic unit. Some sporadic statistics on conservative treatment (mainly from the Scandinavian countries) exceed all but the best American surgical results. The average mortality rates of the total number of cases studied in either group leave little to choose between the two methods. The fact, however, that all the factors of error tend to work in the disfavor of the surgical statistics make it strongly probable that surgical management is superior to the medical mode of treatment as judged by the mortality rate alone.

*This statement must be particularly true of the patients in Vertue's cases that were treated in the outpatient clinic.

TABLE II

MORTALITY IN CONSERVATIVELY TREATED CASES

AUTHOR'S NAME	COUNTRY	YR. OF PUBLICATION	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
Haas	U. S. A.	1922	40	0	0.0
Ibrahim	Germany	1923	400	41	10.2
Meagher	England	1926	22	3	13.5
Schelble	Germany	1926	29	0	0.0
Monrad	Denmark	1938	223	10	4.5
Bischoff	Germany	1929	46	5	10.8
Kemkes	Germany	1929	31	6	19.0
Wolff	Germany	1930	92	10	2.2
Paas	Germany	1932	25	1	4.0
Lindquist	Sweden	1932	43	8	18.6
Behrmann	Germany	1933	25	4	16.0
Faxen	Sweden	1933	126	8	5.5
Munting	Germany	1933	66	11	16.6
Willi	Germany	1933	87	5	5.7
Eckardt	Germany	1934	46	3	6.5
Eckstein	Germany	1934	92	17	18.4
Svensgaard[2]	Denmark	1935	119	9	5.0
Vonderweidt	France	1935	28	5	17.9
Braithwaite[1]	England	1938	21	3	14.3
Dobbs[1]	England	1939	20	3	15.2
Vertue[1]	England	1939	21	0	0.0
Rinvik[2]	Norway	1940	72	2	2.9
Total			1,734	154	8.8

[1]Treated with eumydrine alone.
[2]Treated in part with eumydrine.

TABLE III

LENGTH OF HOSPITALIZATION

AUTHOR'S NAME	SURGICAL (IN DAYS)	MEDICAL (IN DAYS)
Munting	36	76
Paas	42	77
Eckstein	34	91
Eckardt	45	70
Birk	38	78
Rinvik	27	62
Svensgaard*	--	94
Wamsteker	40	79
Average	37.4	78.4

*Medical treatment alone.

TABLE IV

COMPARATIVE MORTALITY RATES

IN PRIVATE AND HOSPITAL CASES

AUTHOR'S NAME	PRIVATE CASES		HOSPITAL CASES	
	NUMBER OF CASES	MORTALITY (PER CENT)	NUMBER OF CASES	MORTALITY (PER CENT)
Bolling	40	2.5	239	15.0
Still	128	10.9	98	56.1
Thompson	31	3.2	178	16.4
Thomson	11	18.2	28	75.0
	210	7.1	543	26.0

This fact, however, could not alone assure priority for the surgical method. If, for instance, Svensgaard's results (in spite of all the possible sources of error therein contained) could be reproduced on a wide scale, his method of treatment would be preferable, provided it equaled the surgical type of management in other respects as well. For it is still a sound principle that, given equal prospects of success, the conservative management of a disease is the one of preference. Such medical results, however, require the utmost in expert nursing, in equipment, and medical attention. It appears an unquestionable fact that a true mortality rate of 5 per cent or less with purely medical measures is a harder task to achieve than a similar surgical mortality rate. Surgical management places a lesser strain on the resources of the average hospital than does medical therapy. Thus a socioeconomic factor enters the discussion and it favors the surgical type of therapy. This therapy has the further important advantage of offering a shorter period of hospitalization (Table III), which on the average is less than one-half that required by the medical method. (In our own series the average hospital stay was 14.8 days, with only one over thirty and five over twenty.) Not only does this mean less cost but also less opportunity for intercurrent infection. (The importance of this factor is well illustrated by Table IV.)

The only sound conclusion from all these considerations is that, as usual, the best road lies in the middle. As formerly emphasized in this study, one must recognize the two main types of the disease: the mild one, eminently suited to conservative management, and the severe one that may, at the expense of much money, time, and patience, be carried through the critical first twelve weeks of life but would be cured by operation quickly and with at least no greater danger to life than the medical management entails. Shanley adds to these two a third group: one that is manageable either medically or surgically. The problem is, then, to make a wise selection and apply the suitable treatment.

In any event, however, it is important to keep in mind that if surgery is to give its best result, the infant should not be carried along stubbornly on a medical regime until its general condition so deteriorates as to make the operative risk prohibitive. Earlier operations have contributed to the prodigious improvement of operative results nearly as much as better preoperative preparation, the two being, in a sense, inseparable (see Table V).

Operative Indications.—The logical way of attacking the problem of selection is to make a trial with conservative management and if this fails within a determined period of time proceed with the surgical intervention. Kirschner, v. Haberer, Heile, and Ramstedt institute medical treatment for three to four days and if this does not produce a definite improvement, recommend operation. Schmid operates if the child is in such poor condition that it cannot withstand a period of

TABLE V

DECLINE OF MORTALITY FROM YEAR TO YEAR

AUTHOR'S NAME	PERIOD OF OBSERVATION	NUMBER OF CASES	MORTALITY (PER CENT)
Bolling	1915-1920	175	17.1
	1923-1925	130	8.5
	1915-1923	125	10.4
Lanman*	1923-1928	150	7.0
	1928-1931	150	2.0
Ladd*	1932-1935	162	4.9
	1936-1939	177	0.56
	1914-1923	81	24.4
Robertson	1924-1933	212	13.0
	1934-1939	109	3.6

*Reports from the same institution (Children's Hospital, Boston).

trial; if the three- to four-day period of medical regime is unsuccessful; or if, in spite of symptomatic improvement, after several days it is still impossible to introduce a sufficient amount of food to assure the resumption of weight gain. Lehmann starts with conservative measures in every case but advises operation if the loss of weight continues after six to eight days. Downes' period of trial is ten days, provided the initial weight loss is less than 20 per cent of the body weight; in the latter case, operation is the method of choice. In seeming contrast Lanman and Mahoney, Donovan, Strauss, and Robertson believe in operation for every case in which the diagnosis of hypertrophic pyloric stenosis has been made. Upon further consideration, this is not as radical as it appears. These men prepare their patients very adequately, therefore they employ two to three days for conservative measures and since the large majority of the patients on conservative trial (at least 80 per cent, Munting) will be found to require operative treatment, only 20 per cent or less of all the patients operated upon by the "all-out surgeons" would theoretically be amenable to a reasonably short medical regime. At any rate, these surgeons have the strong argument in their favor that the number of cases they take out of the pediatrician's hands is small and they are the best risk of all.

Our routine has been similar to that of the more conservative surgeons. After a period of five to six days of the usual medical treatment (hydrating measures, "thick feeding," modified milk formulae, atropine,* and, if necessary, blood transfusion) the patient is operated upon unless a definite improvement of the symptoms has taken place, preferably with some weight gain. According to individual cases this period of trial may vary but it has only twice been longer than ten days, with an average of 4.7 days.

Operative Contraindications.—Before the general acceptance of the surgeon's intervention as a legitimate mode of treatment, the most com-

*We have had no experience with eumydrine.

monly encountered contraindication to operation was the moribund condition of the patient. At the present it is rare to see this picture. One should not operate, also, in the presence of a severe infection, but occasionally exceptions must be made. In infants whose disease began at two months, and particularly three months, of age, conservative treatment is practically always successful; it may be said, therefore, that surgical intervention in most of these cases is unnecessary (Donovan and Shanley).

Preoperative Prognosis.—The all-important prognostic criterion before operation is, of course, the general condition of the infant including its state of nutrition, hydration, and general strength. It follows that the duration of symptoms before operation bears a direct relationship to the mortality rate. Thus, Goldbloom and Spence have found that the mortality of those infants that had had the disease for less than four weeks was only one-third that of the infants suffering from the disease for more than four weeks. Lanman and Mahoney, Tallerman, and McGahee arrived at exactly the same conclusion. The loss of weight at the time of operation is only another way of expressing the same fact; the majority of observers, accordingly, find that the magnitude of weight loss is in linear relationship to the rate of mortality (Goldbloom and Spence: if weight of infant is below 7 pounds, the mortality expectancy is three times higher than in infants weighing more than 7 pounds) (Tallerman, Wallace and Wevill). In general breast-fed infants are in a better position to withstand the operation (Tallerman). Goldbloom's and Spence's conclusions from the analysis of thirty-two postoperative fatalities was that an infant who has been breast fed, who has been ill for less than four weeks, and whose loss of weight is less than 20 per cent of its best previous weight has a mortality expectancy of zero. (It may be mentioned that formerly much was said about Quest's number; this was taken to be one-third of the birth weight of the infant, the loss of which was thought to foretell a sure fatality. It has been shown to be an unreliable criterion.)

It has also been said that the prognosis is poorer the earlier after birth the first symptoms appear (v. Mettenheim, Reiche, Feer, and Langstein). According to Heubner, infants whose disease shows a familial tendency do poorly.

The number of our postoperative deaths is so small that our corresponding data cannot be correlated with the above findings.

Preoperative Preparation.—The above conclusions sufficiently emphasize the obvious importance of restoration of the normal nutritional state of the body to as complete a degree as possible. The results of blood chemical investigations have clearly shown that the chief factors in the metabolic disturbance of the infant are the dehydration and chloride loss. Both can be readily corrected by saline or glucose-saline

infusions.* How profoundly these simple measures have affected the success of surgical treatment is shown by the fact that without exception the great reduction of the mortality rates followed directly after the introduction and popularization of parenteral fluid therapy in the early 1920's (Table V). It can be said without danger of exaggeration that this was as important a factor as the increase in surgical skill.

Prior to operation, preferably on the morning of operation, the stomach should be lavaged. Repeated lavages, however, are to be discouraged. Some prefer to leave a stomach tube in place (Donovan and Spamer), but we find this unnecessary as a routine measure.

Operative Technique.—In general, preoperative medication is seldom used (Bodley and Meader). Shanley recommends seconal, Ramstedt luminal. We find no advantage in using it. The choice of anesthesia has been a somewhat debated point. Opinions are almost equally divided between open ether inhalation (Bolling, Donovan, Ladd, Meredith, Page, Raisch, Ramstedt, Robertson, Strachauer, Thompson and Gaisford, and v. Haberer) and ½ or ¼ per cent novocain local infiltration (Bodley, Kirschner, Meader, Oehler, Pouyanne, Shanley, Vanden Berg, Wallace and Wevill); a few use ethyl chloride (Robertson) or chloroform (v. Haberer, Kehl and Thomann); Spamer operates without anesthesia. The disadvantages of local infiltration are, in our opinion, somewhat more pronounced, namely, the danger of evisceration during operation, the possibility of novocain intoxication (Brown), reduced postoperative wound healing, and increased technical difficulty because of the restlessness of the patient. It is only very seldom that, in our days, one has to operate on a child so debilitated that drop ether inhalation will endanger its life. Brown has pointed out the very considerable danger of novocain intoxication by a simple arithmetic example. The introduction of 20.0 c.c. of ½ per cent novocain into a 5-pound infant is proportionate to the injection into an adult of 150 pounds of 600.0 c.c. of the solution. Our experience has been rather mixed, having used novocain local infiltration twenty-one times and open ether thirteen. During our last eight operations ether was the anesthetic agent.

There have been three main types of incision used in the cases reported: high right rectus (Bodley, Bolling, Clopton and Hartmann, Donovan, Lanman and Mahoney, Oehler, Raisch, Strachauer, Thompson and Gaisford, Wallace and Wevill), high midline (Bodart and Mathieu, Kehl and Thomann, Kirschner, Page, and Spamer) and right subcostal (Pouyanne and Robertson). Meredith uses a right rectus incision but splits the posterior rectus sheath transversely. In our series, fourteen incisions were right rectus muscle-splitting and twenty were high, short midline. The latter type of incision is our personal preference. The most important feature of the incision, however, is

*As a simple illustration of the efficacy of this preparation it may be mentioned that, in spite of the varying but generally persistent vomiting, our patients reached the end of the preoperative period with a net gain of weight (average admission weight 3597 Gm.; average weight at operation 3,744 Gm.).

that it be high and short. A long incision only causes needless evisceration, trauma, and shock without any gain in the facility of operative technique.

The technique of the pyloromyotomy has been, in the overwhelming majority, the Frédet-Ramstedt procedure. The simple steps of this operation have already been outlined. A few additional facts may be here recorded, after the work of Browne on the anatomy of the hypertrophic pylorus. One important feature of the vascular supply of the pylorus is that the superficial arterial branches fail to anastomose at the mid-point from their origin, thus the well-known "bloodless line" is formed. It is important to remember that two deeper vascular branches are almost invariably seen during operation: one, with its accompanying vein is found running across the duodenal end of the incision, just at the important fornix of the mucosa, to which it forms a very useful indication. The other deep vessel appears in the inner layers of the musculature towards the other end of the wound and occasionally causes trouble from bleeding. The generally emphasized rule to remember about the Frédet-Ramstedt operation is that it should be ample in length; the right end of the incision should start about 1 or 2 mm. short of the visible junction between the whitish, opaque, and solid pylorus and the bluish translucent and flaccid duodenum; it should extend well into the pyloric antrum, curving upwards in its left third to follow the bloodless line between the superficial blood vessels. A mere exposure of the mucosa is not enough. At least one-half inch of it should be exposed in the middle of the incision and as much as possible near each end. This is easy except over the zone of adhesions (as mentioned previously) where serosa, muscle, and mucosa split together or not at all. The landmark of the vessel described and the recognition of the annular constriction over the zone of adhesion will prevent injury to the duodenal mucosa here.

In dissecting through the thick muscular wall various maneuvers have been used. V. Haberer and Kirschner cut with one sharp sweep of the knife until mucosa is met. (To facilitate vision, Kirschner used a specially constructed loupe.) Bolling, Downes, Heile, and others deepen the cut about halfway through the muscle layer and thereafter continue with blunt dissection. Lanman and Mahoney, Donovan, and Raisch make the incision just deep enough to penetrate the peritoneal covering and complete the dissection with a blunt instrument, such as a pair of mosquito forceps. Fuchs uses small hooks to pry the edges apart after a shallow sharp incision. Robertson separates the lips of the wound with dissecting scissors.

Among the modifications of the Frédet-Ramstedt technique the Strauss pyloroplasty appears to have been the most successful, at least in the hands of its inventor. Strauss dissects more widely around the mucosa and prepares muscle flaps which he unites above the mucosa. He claims that his cases show much less postoperative distress, mainly vomiting.

Heile makes a counterincision into the pyloric wall, directly opposite the usual location of the incision. Mayo proposes to interrupt the vagus by excising part of the omentum in addition to the standard Ramstedt maneuver. Gohrbrandt advocates the excision of a wedge-shaped piece of the hypertrophied muscular tissue in order to prevent rapid closure that might cause recurrence. Bodley turns a peritoneal flap to cover the wound. Seeger injects saline solution into the pyloric tumor to facilitate its dissection. Ombrédanne, Raybaud (cited by Ramstedt) and Wolfson add a transverse incision to the distal end of the usual longitudinal one. In all these attempts at improvement the greatest value of the Frédet-Ramstedt procedure, its simplicity, is compromised without any increase in efficacy; the operation is merely made more cumbersome and time-consuming.*

Knoflach has carried out extensive experiments on dogs with a view to determining the advisability of modifications in the classical technique of pyloromyotomy. He found no procedure that could equal the advantages of the standard Frédet-Ramstedt operation. He particularly emphasized, as a result of his research, the importance of the location of the incision in the true longitudinal axis of the pyloric canal. If obliquely placed, he found the incision to close over too fast to permit a release of the obstruction.

In our cases the standard Frédet-Ramstedt technique was employed with the exception of one case in which, because of complications in the technical steps, a resection of the pylorus had to be done. The infant recovered nicely. (There have been three other successful pyloric resections for infantile pyloric stenosis reported in the literature. Mátyás, Ritter, and Rupp.)

The commonest complication during the operation is the injury of the duodenal mucosa. This has been reported rather frequently in the literature (Bodart and Mathieu, twice; Bolling, five times; Kohl, six times; Lanman and Mahoney, three times; McLeod, four times; Nissen and Boecker, three times; Oehler, twice; Pouyanne, three times; Raisch, once; Robertson, "a few times"; and Strachauer, twice). The general agreement of opinion is that this mishap does not in itself jeopardize the operative result, provided it is recognized and adequately dealt with. A purse-string suture with some reinforcing Lambert stitches is usually adequate to prevent leakage; it must be remembered that the superior duodenal wall, where this accident invariably occurs, is rather flaccid and has little tendency to leak (Browne). Lamson proposes a plastic flap, prepared from the muscular lips of the wound, to cover up the defect. The best way to treat this danger of technique is, of course, prevention, the rationale of which has been pointed out repeatedly (vide supra). Once the pyloromyotomy is completed, it is wise to test for

*It is noteworthy that in recent times the two obsolete surgical procedures, Loretta's pyloric divulsion and gastroenterostomy, have been revived for use in the treatment of infantile pyloric stenosis by Foramitti and v. Mettenheim, respectively.

an accidental opening by gently pressing the stomach and duodenal contents toward the site of incision. Serious consequences are relatively rare in the literature (Robertson, Kohl, Lanman and Mahoney reported peritonitis resulting in death), but our experience is rather unpleasant with this complication. Among our cases the duodenum was opened in six instances. Of these, one patient made an uneventful recovery; one required resection of the pylorus followed by a Billroth I type of gastroduodenostomy and developed a gastric fistula which healed in 37 days; the third one developed a moderate wound infection, leaving the hospital in 28 days; the fourth became complicated by a duodenal fistula, which eventually cleared up but required 24 days of hospitalization; the fifth one continued to vomit intermittently for about 22 days from causes that apparently had no direct relationship to the duodenal accident; in the last one, the wound healed rather slowly and convalescence was sluggish but no direct effect of the mishap could be noted. In four of these cases, drainage was instituted—the only cases in which we did this—and these four did the least well, two of them developing fistulas. Briefly then, from our experience, accidental opening of the duodenal mucosa, even if recognized and repaired immediately, forecasts the probability of a stormy postoperative course, particularly if drain is used in closure, but does not seriously influence the long-range results or mortality rate.

As a complication encountered during operation one may also mention the failure to find a pyloric tumor. The etiologic and diagnostic implications of this phenomenon have already been discussed. The absence of the pyloric tumor should not preclude the performance of the Frédet-Ramstedt operation. These cases invariably manifest severe and typical preoperative symptoms, frequently entirely refractory to medical measures. Downes (two cases), Kirschner, Lanman and Mahoney, Mouriquand and Weill (two cases), and Thompson and Gaisford found a dramatic improvement after the carrying out of the typical pyloromyotomy. Although Higgins warns against any operative procedure on the pylorus in these cases, there can be little doubt that the easiest course is to carry out the pyloromyotomy, except in cases where the diagnosis was questionable, cases that should not as a rule come to the operating table in any event. V. Mettenheim goes as far as advocating pyloromyotomy for certain cases of a pure "gastrospasm," that is persistent vomiting without organically demonstrable pyloric change. (Of course, in all such cases one must exclude the possibility of some other organic lesion by careful exploration.)

There has been slight variation in the technique of closure as reported in the literature. All authors insist on careful suturing in layers. About the only important exception to this is Lee's practice, who uses through-and-through inabsorbable sutures; he claims that his postoperative wound healing has been much improved by this method. The suture material has been catgut in all instances where mention is made of it,

with the exception of Ladd, who uses silk. Some (Clopton and Hartmann) use inabsorbable suture material for stay sutures while using catgut for the rest of the closure. We close in careful layers and have used catgut fifteen times and silk eighteen times (in one case our record does not specify the suture material); for the past three years we have employed silk alone. Our number of wound infections was too small to be correlated with the suture material used.

Postoperative Course and Treatment.—The majority of infants continue to vomit to a lesser or greater extent for a short period of time after operation. In general this time is found to be around two to three days (Page). Munting observed complete cessation of vomiting immediately after operation in only 28 per cent of his cases, and Eckstein in only 38 per cent of his cases. There have been various explanations proposed for this postoperative vomiting. V. Haberer, for instance, states that most of the cases manifesting this postoperative symptom show blood in their vomitus preoperatively; thus, the presence of mucosal lesions would be presupposed that require time for healing. Others claim (v. Mettenheim) that these infants are particularly excitable, i.e., in their cases the central nervous factor is particularly prominent. An explanation near at hand would be to presume that in these cases the pyloromyotomy was not complete enough. From the findings at reoperation reported by Fröhlich, Gaisford, Hess, Nobel, Noetzel, and Sauermondt, Ramstedt argues that this is not the case. His explanation of the phenomenon of temporary postoperative vomiting and of the total failure of the operation to cure will be discussed briefly later. Dietrich contends that the kinking of the duodenum brought about by the dilatation of the body of the stomach which, consequently, assumes a lower position, is responsible for the postoperative persistence of vomiting. As Ramstedt points out, this must be a rare factor. Without looking for controversial reasons, however, and simply considering that most of these infants have been vomiting for three weeks or more before operation, one would expect that a period of readjustment will be necessary after the obstruction has been overcome. The rapidity of readjustment of the disturbed emptying mechanism is, in fact, surprising in the large majority of cases.

Because of this period of readjustment it has been suggested by Faber and Davis that postoperative feeding be started twenty-four or forty-eight hours after the time of operation in order to provide a physiologic rest for the stomach. These authors claim to have shown that there is a reduction of motility of the stomach for two to five days postoperatively, demonstrable by roentgenograms and fluoroscopy. The soundness of delayed feeding, however, has been questioned by all the most experienced surgeons (Robertson). The universal custom is to resume feeding very soon after operation, the interval varying from a few minutes to four hours. Exception should be made in cases of perforation of the duodenum where the feeding schedule may preferably start twenty-four hours later than usual.

The composition of the diet fed postoperatively varies widely. Modification of cow's milk, breast milk, whey, and combinations of these are used. The important principles are the very gradual increase in amounts and the careful selection and timing of the new articles introduced.

The usual supportive measures (parenteral fluids, blood transfusion, etc.) are now universally used. It is also a universal practice to entrust the regulation of the postoperative feeding to the pediatrician.

Almost always after the surgical intervention a moderate temperature elevation is noted (Munting, Rohmer, and Strauss), which is a more accentuated counterpart of the similar finding in adults and which subsides in two to three days. It is more pronounced than in the adult probably because of the differences in the physiologic response.

In our series the vomiting ceased gradually on the second or third day in the largest number of cases (57 per cent). In one case vomiting never occurred postoperatively, and in one after the eighth postoperative hour; in five, it stopped during the first twenty-four hours; in two, within four days; in one, within five days. One patient continued to vomit for ten days, one for twenty-two days and one for twenty-three days. In twenty-three of our cases (excluding the fatal ones) there was a postoperative temperature elevation of 100° F. or more. This, however, was higher than 102° in only seven cases and only in one instance did it last more than two days. The average discharge weight was 3968 Gm., which signifies an average postoperative gain of 224 Gm.

Postoperative Complications.—Causes of Death: The postoperative complications directly attributable to the surgeon's intervention are peritoneal infection, wound infection and wound separation, hemorrhage from the pyloric or abdominal wound, anesthetic complications, shock and such intra-abdominal complications as adhesions or volvulus (Ramstedt). In the same group one should also include deficient postoperative results, but these will be discussed under a different heading.

In analyzing these complications, it should be borne in mind that no accurate figures are available in the literature in regard to their milder forms and that whatever figures are quoted are taken from mortality statistics.

Peritonitis is more common than the reports on the incidence of duodenal perforation would lead one to expect. Obviously, either a large proportion of the accidental injury of the duodenal mucosa is not recognized or some other, as yet unidentified, source of infection must be responsible. Peritonitis in these infants is always fatal; it forms about 10 per cent of all the postoperative fatalities.

It has been many times noted that wounds in stenotic infants, although in general not especially prone to develop severe infections, have a tendency to imperfect and delayed wound healing, with thin serous drainage and stitch abscesses (McGahee). Thus, evisceration or simple wound disruption has been reported in higher percentage of these cases than of other surgical procedures in infants (Bodley, Lanman and

Mahoney, Page, and Rohmer). The obvious reason for this behavior has been suggested to be the poor nutritional state of the infant. Ladd believes, but is unable to quote quantitative proofs, that the blood vitamin C level must be subnormal in these infants and recommends prophylactic administration of this substance. That adequate preoperative preparation of the infant has an important bearing on the occurrence of wound disruption can be gathered from its markedly lower incidence in the more recent reports. In this connection it should be mentioned that postoperative hernias are quite rare in these patients (Bolling).

Many authors (v. Haberer and Ladd) consider postoperative hemorrhage the most dreaded complication. The bleeding may take place from the pyloric incision (Bolling) or from the abdominal wound (Mouriquand and Weill, and Bolling). Painstaking hemostasis in the wall of the pyloric canal has been insisted upon by these surgeons, although others believe that if the incision is properly placed the danger of bleeding is negligible with no hemostasis whatever (Browne and Meredith). In any event, postoperative hemorrhage is an important cause of death, being responsible for about 5 per cent of all postoperative deaths.

Anesthetic complications, postoperative pneumonia and pulmonary atelectasis, following pyloromyotomy often are not purely surgical misfortunes. As has been pointed out repeatedly, this operation is such a light procedure that it taxes the infant's physical resources only slightly (Lanman and Mahoney, Bodley, Thompson and Gaisford, Wyatt). In the large majority of cases a greater share of the responsibility must be referred to the debility of the child caused by preoperative delay or lack of preparation. These complications form the largest single source (about 10 to 15 per cent) of fatalities in the large early collections of cases.

Much the same argument holds true for postoperative shock. Its frequency as cause of death was about on par with or slightly below that of postoperative pulmonary complications.

Postoperative adhesions, volvulus, or other forms of intestinal obstruction are rare. Their incidence has not apparently changed with the changing results of operative treatment.

The not strictly surgical complications after pyloromyotomy are gastroenteritis and terminal inanition, also called decomposition or atrophy. A comparison of these postoperative mishaps with the true surgical complications yields interesting conclusions. In Table VI the largest published collection of fatalities (Ramstedt) is grouped in three classes. Group 1 contains the so-called nonsurgical causes, i.e., those that have their origin in the debilitated general condition of the infant. These infants were practically moribund when they reached the operating table. In Group 2 are comprised the causes that are partly surgical—at least insofar as pulmonary complications are concerned—

TABLE VI

CAUSES OF DEATH IN 143 SURGICALLY TREATED CASES

(RAMSTEDT)

GROUP	NATURE OF CAUSE OF DEATH	NUMBER OF CASES	(PER CENT)
1	Extreme physical weakness before operation, leading to decomposition, atrophy, collapse or inanition postoperatively	58	40.5
2	Intercurrent postoperative infection, viz., broncho-pneumonia, gastroenteritis, influenza	35	24.5
3	Postoperative complications proper, viz., operative shock, hemorrhage, peritonitis, wound infection	50	35.0

but also either partly or mainly, as in cases of gastroenteritis, medical. Finally, in Group 3 are arranged the purely surgical causes formerly discussed. As has already been said, the responsibility for the pulmonary complications is debatable; gastroenteritis, on the other hand, is certainly a predominantly medical problem. Among other facts, its being reported most frequently from the crowded, poorly protected English infants' wards bears this out clearly. If one now makes an approximate calculation, and such is the only calculation one can make, one finds that at least half of all the postoperative fatalities are ultimately due to medical causes. This fact throws fresh light on the debate about the respective merits of the surgical and medical types of treatment on grounds of mortality statistics (vide supra).

In analyzing postoperative complications and causes of death, it is well to remember that, properly speaking, the discussion should be largely in the past tense. The picture has so radically changed in the last ten years that the figures quoted above, and used because they are the only available ones, hardly apply to present conditions. The only postoperative complication that has remained relatively unaltered in its frequency is infection (peritoneal and of the wound), but even infection has lost much of its importance as a lethal factor. Because of the changed operative indications, because of the realization of the importance of preoperative preparation, and because of the improved hygiene of the infants' ward, the medical causes of postoperative complications have become markedly reduced. Besides infection, the only operative dangers of consequence the infant now faces are shock, pneumonia, and technical mistakes, a minimum of which will persist by reasons inherent in the very nature of surgery.

Among our own patients, in two instances (7 per cent) moderately severe wound infection developed but no wound disruption occurred. Mild wound infection (i.e., stitch abscess) was noted in nine instances (32 per cent). We practice careful hemostasis throughout, and perhaps for this reason have had no postoperative hemorrhages. There were two fatalities (mortality rate 5.9 per cent).* One of these patients was

*Recently another successful case has been added to this series, changing the operative mortality to 5.8 per cent.

operated upon in the presence of an evident severe respiratory infection and died in twenty-four hours, of bronchopneumonia. Autopsy left no doubt that the pneumonia had been present when the operation was undertaken. Operative intervention had, however, been considered the lesser of the risks. The other lethal case was one of a purely surgical death—peritonitis on the fifth postoperative day. During operation no viscus had been perforated and this fact was confirmed by the necropsy findings.

Operative Results.—The worth of an operation can be measured by the double standard of immediate and late results.

In judging the immediate results of the Frédet-Ramstedt operation it would be desirable to proceed on the basis of some definite criteria of success, but, unfortunately, such criteria have never been established and, indeed, are probably impossible to define. The data most generally accepted as denoting success are the cessation of weight loss and resumption of gain of weight within a resonably short time postoperatively; conversely, when this fails to take place, the operation is a failure. Although this length of time varies widely, in some cases perhaps embracing such a long period that the point of beginning of improvement may fall outside the limits of true operative cure, one must accept the judgment of the surgeon who is called upon to decide whether a secondary operation is necessary. When the surgeon acknowledges that reoperation is indicated, he recognizes that the first operation was a failure. By this standard, then, all patients who survive without reoperation are taken to be successes. This index of operative success is broad but fairly reliable, and it is the only one available. In assessing the number of reoperations one must exclude the cases of gross and obvious technical error and the cases of mistaken diagnosis not recognized at the time of the first operation. The gross rate of reoperation will thus be about 3 per cent, with a corrected incidence of about 2 per cent (Fröhlich, Gaisford, Hess, Lanman and Mahoney, Nobel, Nötzel, Page, Ramstedt, Rinvik, Sauermondt). The rate of immediate satisfactory results of the Frédet-Ramstedt operation is, therefore, 97 to 98 per cent, less the number of operative fatalities which at the present time can be placed between 1 and 2 per cent. This is a result unexcelled by any other major operative procedure.

At this juncture the question arises, What is the cause of the failures not accounted for by gross technical error and error in diagnosis?

In the absence of definite knowledge with respect to the cause and pathogenesis of infantile pyloric stenosis, the answer must be one of speculation. Taking into consideration all the etiologic possibilities, the Frédet-Ramstedt operation may have its point of attack on any one or more of the following four anatomic planes: (1) the sphincter pylori; (2) the hypertrophic musculature of the pyloric canal; (3) the nerve pathways in the wall of the pyloric canal and perhaps also in the sphincter itself; and (4) the submucosa and mucosa (by permitting

their full unfolding). The opinion is practically unanimous that the effect on the mucosa and submucosa is of secondary importance. Likewise, there is general agreement in regard to the great importance of the completeness of the section of the hypertrophic pyloric musculature. The advice is constantly stressed that the incision should be carried high on to the gastric wall, as close to the boundary of the duodenum as practicable, and as far down as the level of the submucosa. (Unquestionably the "gross errors of technique" mentioned above result from the disregard of these cautions.) Curiously, however, many surgeons (Hess, Nobel, Nötzel, Ramstedt, and Sauermondt) have remarked that at reoperation the incision in the pyloric wall is usually found ample in terms of gross anatomy. There would, then, remain two possible explanations for the initial failure. One would be the assumption that the nervous pathways involved in the causation of the disease have not been adequately severed. It does not, indeed, seem unreasonable to postulate that the disruption of some as yet unidentified nerve fibers has some bearing on the operative result, although the exact nature and the precise extent of this relationship is not at all clear. It is less compatible with logical thinking, however, to accept the intactness of these hypothetical nerve paths as the sole and full source of the persistence of plyoric obstruction. Much more in keeping with sound reasoning is the second possible supposition, i.e., that in a certain proportion of cases the sphincter pylori is not included in the pyloric incision. This structure, it will be remembered, does not partake in the hypertrophy of the pyloric musculature; its location thus becomes rather hidden and its proper cleavage is made the more difficult owing to the dangerous "zone of adhesions" directly adjacent to it. Proceeding on the theory of Lehmann, it may be presumed that the unsectioned sphincter will continue to offer resistance to passage through the pyloric opening, although to the naked eye the separation of the hypertrophic muscle bundles appears sufficient. In discussing the problem of operative failures Ramstedt likewise considers the accidental omission of the sphincter from the incision as the important factor. However, not subscribing fully to Lehmann's theory, he assumes that this omission, which he believes to be very common, is of no consequence in the majority of cases; occasionally, though, it will lead to a persistence of the preoperative symptoms. In support of the interpretation according to Lehmann's theory one may mention further that a second operation, which invariably consists of an enlarging of the original incision and thus affords a better opportunity to sever the sphincter, as a rule results in prompt relief of the symptoms.

The role of central nervous factors in the evolution of the disease picture of infantile pyloric stenosis must be borne in mind when discussing poor operative results. In a very few cases these may presumably be so preponderant as to preclude the possibility of complete cure by mechanical means alone.

The long-range results of plyoromyotomy can be studied in the numerous follow-up investigations made with the view of determining the presence or absence of possible etiologic factors. The conclusions of these extensive works of research are in general agreement (Mouriquand and Weill, Oehler, Rinvik, Runström, Schlesinger, Strauss, Uhr, Wamsteker, and Wyatt) that, by practically all standards of testing, these patients are, in their later life, as normal as any comparable group of persons from the general population. Certain roentgenologic signs persist to indicate the site of the former abnormality (Runström, Viethen, and Andresen), but even these tend to disappear after puberty and, in any event, have no apparent clinical significance.*

Among our own cases, the immediate results consisted of thirty complete cures, one partial cure, and one failure (exclusive of the two fatal cases). A reoperation in the partially cured case brought about a very satisfactory permanent result. The instance of failure was probably the effect of mistaken judgment. This patient had a history of over a year of persistent vomiting, refractory to all forms of conservative management. Operation was undertaken as a long-chance attempt to help him. A reoperation elsewhere was also unsuccessful. As the child grew older it became evident that he was feeble-minded and what had been taken for persistent vomiting had in fact been rumination.†

SUMMARY AND CONCLUSIONS

On grounds of the pertinent literature of the past fifty years—with special attention paid to that of the past twenty years—and with the help of the clinical analysis of thirty-four cases treated in the division of general surgery of the Henry Ford Hospital, the problems of etiology, symptomatology, and diagnosis of infantile pyloric stenosis have been briefly surveyed and its surgical treatment more exhaustively discussed.

From the best evidence extant it appears that infantile pyloric stenosis is probably the result of achalasia of the sphincter pylori. The gross pathologic lesion represents a form of work hypertrophy of the musculature of the pyloric canal. Strong secondary central nervous factors play a part in the coloring of clinical manifestations. There is strong evidence that in the etiology of the disease a hereditary factor plays an important part. The preponderance of males, first-born infants, and members of the so-called Nordic races among the patients is real but its etiologic meaning is not understood.

Persistent forceful vomiting, palpable pyloric swelling, visible peristalsis of the stomach, loss of weight, hypochloremia, hypochloruria, and obstipation are the cardinal findings. Of these only the palpable pyloric tumor has pathognomonic significance, but it is frequently absent.

*It should be added that the late results of cases managed by medical means are as good as those of the operative cases.

†As to late results, our investigation is now in progress.

The roentgenographic appearance of the pyloric canal is the only infallible diagnostic sign.

So-called pylorospasm is most likely not an entity. The term is admissible but superfluous for designating a mild, nonsurgical form of stenosis. It should be discarded as a cover-all of nondescript vomiting attacks.

The disease is easily curable by medical means in its mild form; manageable, but at prohibitive expense of time, energy and money, by medical means in most of its more severe forms; it is easily curable in all its grades by surgical means. Medical treatment should be restricted to mild cases but should be given a trial in all but the most severe cases.

Adequate preparation of the patient before operation is a factor as important as the skill of the surgeon, or perhaps more so. The Frédet-Ramstedt operation, or pyloromyotomy, has no equal among the other surgical procedures proposed. If the simple but rigorous rules of its technique are followed it is one of the most nearly ideal operations known, with a mortality rate of less than 2 per cent and a rate of cure of at least 95 per cent. The commonest pitfalls in its performance are the injury of the duodenal mucosa and incomplete cleavage of the sphincter pylori. The latter is the most probable cause of the rare operative failures. Ether inhalation anesthesia, midline epigastric incision, careful hemostasis, and silk suturing are technical aids of choice.

Synopsis

of 34 Surgically Treated Cases of Infantile Pyloric Stenosis Seen in the Henry Ford Hospital in the Years 1922-1941

Distribution by decades:

1922-1930	10 cases
1931-1941	24 cases

Sex distribution:

Males	29 (85.3%)
Females	5 (14.7%)

Race:

All white.—31, Celti-Anglo-Saxon; 1, Polish; 1, Russian; and 1, Hungarian

Prenatal history, birth:

All pregnancies normal, full term; all deliveries normal, except:

1. Face presentation
2. Vertex presentation, low forceps
3. Cervical cesarean section for funnel pelvis
4. Footling breech
5. Low forceps (cause?)

Order of birth:

First born	18 (58%)
Others	13 (42%)
No data	3

Feeding history:

Breast	22 (75.8%)
Mixed	1 (3.5%)
Bottle	6 (20.7%)

(No data, "vomiting since birth" 5)

Age at onset:

Birth	4
First week	4
Second week	6
Third week	6

Month of onset:

Jan.-Feb.-Mar.	5 cases
Apr.-May-June	6 cases
Jul.-Aug.-Sept.	17 cases
Oct.-Nov.-Dec.	6 cases

Duration of symptoms:

Mean	18.3 days
Longest	60.0 days
Shortest	2.0 days

SYNOPSIS—CONT'D

Fourth week	5
Fifth week	2
Sixth week	3
Seventh week	0
Eighth week	1
No data	3

ASSOCIATED DISEASES:

One indirect inguinal hernia
One thrush
One impetigo

PROJECTILE VOMITING:

Present	31
Absent	1
No data	2

VISIBLE GASTRIC PERISTALSIS:

Present	26
Absent	6
No data	2

PALPABLE PYLORIC "TUMOR":

Present	17
Absent	13
No data	4

BLOOD IN VOMITUS:

Present	1
Absent	30
No data	3

LENGTH OF CONSERVATIVE PREOPERATIVE TREATMENT:

Mean	4.7 days
Only two cases over	10 days

ANESTHESIA:

Ether	13
Local—Novocain ½% —Novocain ¼%	21

In last 3 years: Ether alone

INCISION:

Right rectus	14
Epigastric midline	20

Of last 22 cases only 5 right rectus

TYPE OF OPERATION:

Frédet-Weber-Ramstedt	33
Resection of pylorus, Billroth I, gastroduodenostomy	1

WOUND CLOSURE:

All in layers
Four drained:

1. Duodenal perforation; duodenal fistula—60 days' hospitalization
2. Duodenal perforation; healing satisfactory
3. Duodenal perforation; resection of pylorus; gastric fistula—37 days' hospitalization
4. Duodenal perforation; intermittent vomiting for 22 days; final result satisfactory

SUTURE MATERIAL:

Catgut	15
Silk	18
No data	1

In last 3 yrs. only silk used

WOUND INFECTION:

Superficial	9
Deep (but without separation)	2

(Excluding cases in which drainage was used and fatal cases)

OPERATIVE FINDINGS:

Typical appearances of pylorus in 32 cases.

In one, no true pyloric swelling was present. Pylorus was firm and hard due to spasm. Standard Frédet-Weber-Ramstedt procedure brought complete cure.

In another, pylorus showed very slight hypertrophy. Pyloromyotomy brought no improvement. This case was later diagnosed as rumination.

POSTOPERATIVE COURSE OF 6 PATIENTS WITH ACCIDENTAL PERFORATION OF THE DUODENAL MUCOSA

(1) Uneventful recovery; postoperative stay 15 days.

(2) Excision of pylorus; Billroth I, drainage, gastric fistula; postoperative stay 37 days.

(3) Slight wound infection, recovery otherwise smooth; postoperative stay 28 days.

(4) Drainage, duodenal fistula; postoperative stay 24 days.

(5) Drainage, slight serous drainage, otherwise healing satisfactory; vomiting for 22 days.

(6) Wound healed well, no drain; vomiting subsided slowly after 23 days.

SYNOPSIS—CONT'D

POSTOPERATIVE FEVER:

Exclusive of fatalities:
Temp. of 100° F. or more in 23 cases
Of these, only one longer than 24 hr.
Temp. above 102° F. in 7 cases

CESSATION OF VOMITING:

Exclusive of fatalities:	
Immediately P. O.	1
8 hr. P. O.	1
24 hr. P. O.	5
2 to 3 days P. O.	18
4 days P. O.	2
5 or more days P. O.	5

LENGTH OF POSTOPERATIVE HOSPITALIZATION:

Mean	14.8 days
Five	More than 20 days
One	More than 30 days

OPERATIVE RESULTS:

Complete cure 30 cases*
Reoperation necessary 2 cases
One: Here with complete cure
One: Elsewhere with poor result
(Diagnosis probably incorrect)
Deaths 2 cases
1 Peritonitis fifth postoperative day
1 Ba. pneumonia 24 hr. postoperatively

SUMMARY OF X-RAY FINDINGS (20 CASES)

Tone:		Size:		Peristalsis:		3-hour retention:	
Hypo	9	Large	7	Hypo	9	90% or more	16
Normal	3	Normal	2	Normal	3	80%	1
Hyper	1	Small	1	Hyper	4	75%	1
No data	7	No data	10	No data	3	60%	1
				Reverse	1	30%	1

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*Recently another successful case has been added to this series.

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Book Reviews

The Care of the Aged. By Malford W. Thewlis. Ed. 4, Pp. 589, with 35 illustrations. St. Louis, 1942, C. V. Mosby Co.

The fourth edition of this standard work gives evidence of its popularity. It is certainly the best book of its kind in English, but it would be an even better one if it were one-half as long. The latter half of the book contains little about the treatment of specific disorders which is not covered much more satisfactorily in standard reference work, but the earlier chapters dealing with the broader aspects of geriatrics are sympathetic and helpful. Every practitioner will be a better physician for having read the first twenty chapters. Until the degenerative lesions of senescence are much better understood than they are today, however, it seems extravagant to feel that geriatrics can be as useful a specialty as pediatrics. Certainly, it has accomplished nothing as yet which permits comparison.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgement of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

PHYSICAL DIAGNOSIS. By Cabot and Adams—F. Dennette Adams, M.D., Harvard Medical School. Cloth. Price $5.00. Pp. 888, with 398 illustrations. Baltimore, 1942, Williams and Wilkins Company.

STANDARD NOMENCLATURE OF DISEASE AND STANDARD NOMENCLATURE OF OPERATIONS. By American Medical Association, Edwin P. Jordan, M.D., editor. Cloth. Price $3.50. Pp. 1022. Chicago, 1942, American Medical Association.

DIAGNOSTICO DE LOS TUMORES ABDOMINALES, vol. 2. By Pablo L. Mirizzi, De Ciencias Medicas do Cordoba. Cloth. Pp. 1280, with 381 illustrations. Buenos Aires, 1941, Libreria "El Ateneo."

THE HAND: ITS DISABILITIES AND DISEASES. By Condict W. Cutler, Jr., M.D., F.A.C.S., Associate Surgeon, Roosevelt Hospitals, Division of Surgery, Welfare Hospital, New York. Cloth. Pp. 572, with 274 illustrations. Philadelphia and London, 1942, W. B. Saunders Company.

A TEXTBOOK OF GYNECOLOGY. By Arthur Hale Curtis, M.D., Northwestern University. Cloth. Pp. 723, with 401 illustrations. Philadelphia, 1942, W. B. Saunders Company.

SURGERY CLINIC OF NORTH AMERICA—SYMPOSIUM ON INDUSTRIAL SURGERY. By many contributors. Cloth. Pp. 300, with 80 illustrations. Philadelphia, 1942, W. B. Saunders Company.

MEDICAL PROGRESS ANNUAL, vol. 3. By Robert N. Nye, M.D., Boston. Cloth. Price $5.00. Pp. 678. Springfield, Ill., 1942, Charles C Thomas, Publisher.

OXFORD MEDICAL OUTLINE SERIES; MINOR SURGERY. By Charles M. Oman, M.D. Cloth. Pp. 165. New York, 1942, Oxford University Press.

WESTERN SURGICAL ASSOCIATION TRANSACTIONS. By Harry B. Zimmermann, M.D., Recorder. Cloth. Pp. 569, with 50 illustrations. St. Paul and Minneapolis, 1942, The Bruce Publishing Company.

A SHORT HISTORY OF CARDIOLOGY. By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College, Chicago. Cloth. Price $3.50. Pp. 258, with 48 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

CLINICAL ANESTHESIA—A MANUAL OF CLINICAL ANESTHESIOLOGY. By John S. Lundy, M.D., Mayo Clinic. Cloth. Pp. 771, with 266 illustrations. Philadelphia and London, 1942, W. B. Saunders Company.

FIRST AID—SURGICAL AND MEDICAL. By Warren H. Cole, M.D., F.A.C.S., Professor of Surgery, University of Illinois, Chicago, and Charles B. Puestow, M.D., Ph.D., F.A.C.S., Chicago. Cloth. Pp. 351, with 92 illustrations. New York and London, 1942, D. Appleton-Century Company, Inc.

ABDOMINAL AND GENITO-URINARY INJURIES. By Military Surgical Manuals, National Research Council. Cloth. Pp. 243, with 28 illustrations. Philadelphia, 1942, W. B. Saunders Company.

OPHTHALMOLOGY AND OTOLARYNGOLOGY. By Military Surgical Manuals, National Research Council. Cloth. Pp. 331, with 51 illustrations. Philadelphia, 1942, W. B. Saunders Company.

ROENTGEN TREATMENT OF DISEASES OF THE NERVOUS SYSTEM. By Cornelius G. Dyke, M.D., F.A.C.R., and Leo M. Davidoff, M.D., F.A.C.S., Columbia University-Jewish Hospital, Brooklyn. Cloth. Price $3.25. Pp. 198, with 12 illustrations. Philadelphia, 1942, Lea and Febiger.

CHANGES IN THE KNEE JOINT AT VARIOUS AGES. By Granville A. Bennett, M.D., Hans Waine, M.D., and Walter Bauer, M.D., Harvard Medical School. Cloth. Price $2.50. Pp. 97, with 31 illustrations, New York, 1942, Commonwealth Fund.

BLOOD SUBSTITUTES AND BLOOD TRANSFUSIONS. By Stuart Mudd, M.A., M.D., Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and William Thalhimer, M.D., Division of Human Serum, Public Health Research Institute of New York. Cloth. Price $5.00. Pp. 407, with 94 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

THE SURGERY OF PANCREATIC TUMORS. By Alexander Brunschwig, M.D., F.A.C.S., Professor of Surgery, University of Chicago. Cloth. Pp. 421, with 123 illustrations. St. Louis, 1942, C. V. Mosby Company.

THE MAKING OF A SURGEON. By Ernest V. Smith, M.D., D.Sc., F.A.C.S. Cloth. Price $3.00. Pp. 344, with 41 illustrations. Fond du Lac, Wisconsin, 1942, Berndt Printing Company.

SURGICAL PATHOLOGY. By William Boyd, M.D., LL.D., M.R.C.P. (Ed.), F.R.C.R. (London), Professor of Pathology, Toronto. Cloth. Pp. 843, with 504 illustrations and 16 color plates. Philadelphia, 1942, W. B. Saunders Company.

MANUAL OF DERMATOLOGY. By Donald M. Pillsbury, M.D., Marion B. Sulzberger, M.D., and Clarence S. Livingood, M.D. Cloth. Pp. 421, with 109 illustrations. Philadelphia, 1942, W. B. Saunders Company.

WAR MEDICINE. By editor, Winfield Scott Piegh, M.D., Commander (M.C.) U.S.N., formerly Surgeon, City Hospital, New York. Cloth. Pp. 565, with 76 illustrations. New York, 1942, F. Hubner and Company, Inc.

LYMPH NODE METASTASES: INCIDENCE AND SURGICAL TREATMENT IN NEOPLASTIC DISEASE. By Grantley Walder Taylor, M.D., Institute of Surgery, Harvard. Cloth. Price $8.00. Pp. 498, with 61 illustrations. New York, 1942, Oxford University Press.

THE HEMORRHAGIC DISEASES AND THE PHYSIOLOGY OF HEMOSTASIS. By Armand J. Quick, Ph.D., M.D., Associate Professor of Pharmacology, Marquette University School of Medicine, Milwaukee, Wis. Cloth. Price $5.00. Pp. 340, with 24 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

SULFANILAMIDE AND RELATED COMPOUNDS. By Wesley W. Spink, M.D., F.A.C.P. Cloth. Price $3.00. Pp. 374. Chicago, 1942, The Year Book Publishers, Inc.

THE HOSPITAL CARE OF THE SURGICAL PATIENT. By George Crile, Jr., M.D., and Franklin L. Shively, Jr., M.D., Cleveland Clinic, Cleveland. Leather finish. Price $2.50. Pp. 184, with 21 illustrations. Springfield, 1943, Charles C Thomas, Publisher.

THE BIOLOGICAL ACTION OF THE VITAMINS, A SYMPOSIUM. By E. A. Evans, Jr., University of Chicago. Cloth. Pp. 227, with 20 illustrations. Chicago, 1942, University of Chicago Press.

SURGICAL CLINICS OF NORTH AMERICA, Dec., 1942, vol. 22. By many contributors. Cloth. Pp. 300, with 66 illustrations. Philadelphia, 1942, W. B. Saunders Company.

SURGICAL CLINICS OF NORTH AMERICA, Oct., 1942, vol. 22. By many contributors. Cloth. Pp. 261, with 63 illustrations. Philadelphia, 1942, W. B. Saunders Company.

FRACTURES. By Paul B. Magnuson, M.D., F.A.C.S., Northwestern Medical School, Chicago. Cloth. Price $5.50. Pp. 511, with 319 illustrations. Philadelphia, 1942, J. B. Lippincott Company.

ORTHOPEDIC SUBJECTS. By Military Surgical Manuals, National Research Council. Cloth. Pp. 306, with 77 illustrations. Philadelphia, 1942, W. B. Saunders Company.

THE YEAR BOOK OF INDUSTRIAL AND ORTHOPEDIC SURGERY 1942. By Charles F. Painter, M.D., Massachusetts Women's Hospital, Boston. Cloth. Price $3.00. Pp. 424, with 300 illustrations. Chicago, 1942, The Year Book Publishers.

MANUAL OF OXYGEN THERAPY TECHNIQUES. By Albert H. Andrews, Jr. Cloth. Price $1.75. Pp. 191, with 30 illustrations. Chicago, 1942, The Year Book Publishers.

ORTHOPEDIC SUBJECTS. By Military Surgical Manuals, National Research Council. Cloth. Price $3.00. Pp. 306, with 79 illustrations. Philadelphia, 1942, W. B. Saunders Company.

TREATMENT OF FRACTURES. By Guy A. Caldwell, M.D., F.A.C.S., University of Louisiana School of Medicine. Cloth. Price $5.00. Pp. 303, with 92 illustrations. New York, 1943, Paul B. Hoeber, Inc.

BURNS, SHOCK, WOUND HEALING AND VASCULAR INJURIES. By Military Surgical Manuals National Research Council. Cloth. Price $2.50. Pp. 272, with 80 illustrations. Philadelphia, 1943, W. B. Saunders Company.

RENAL LITHIASIS. By Charles C. Higgins, M.D., Cleveland Clinic, Cleveland. Cloth. Price $3.00. Pp. 140, with 18 illustrations. Springfield, Ill., 1943, Charles C Thomas, Publisher.

PRINCIPLES AND PRACTICES OF OBSTETRICS. By Joseph B. DeLee, M.D., Consultant in Obstetrics, Chicago Lying-in Hospital and Dispensary, and J. B. Greenhill, M.D., Attending Obstetrician, Michael Reese Hospital, Chicago. Cloth. Price $10.00. Pp. 1101, with 841 illustrations. Philadelphia, 1943, W. B. Saunders Company.

ESSENTIALS OF PROCTOLOGY. By Harry E. Bacon, M.D., F.A.C.S., F.A.P.S., Head of the Department of Proctology, Temple University. Cloth. Price $3.50. Pp. 345, with 168 illustrations. Philadelphia, 1943, J. B. Lippincott Company.

DISEASES OF THE NOSE, THROAT AND EAR; MEDICINE AND SURGERY. By William L. Ballenger, M.D., F.A.C.S., Late Professor and Head of Department of Otology, Rhinology and Laryngology, University of Illinois, Chicago, and Howard Charles Ballenger, M.D., F.A.C.S., Associate Professor of Otology, Northwestern School of Medicine, Chicago. Cloth. Price $12.00. Pp. 975, with 604 illustrations. Philadelphia, 1943, Lea & Febiger.

NEUROSURGERY AND THORACIC SURGERY. By Military Surgical Manuals, National Research Council. Cloth. Price $2.50. Pp. 310, with 97 illustrations. Philadelphia, 1943, W. B. Saunders Company.

SURGERY CLINICS OF NORTH AMERICA. By many contributors. Cloth. Pp. 312, with 77 illustrations. Philadelphia, 1943, W. B. Saunders Company.

GYNECOLOGY INCLUDING FEMALE UROLOGY. By Lawrence R. Wharton, Ph.B., M.D., Associate in Gynecology, The Johns Hopkins Medical School; Assistant Johns Hopkins. Cloth. Pp. 1006, with 444 illustrations. Philadelphia, 1943, W. B. Saunders Company.

To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

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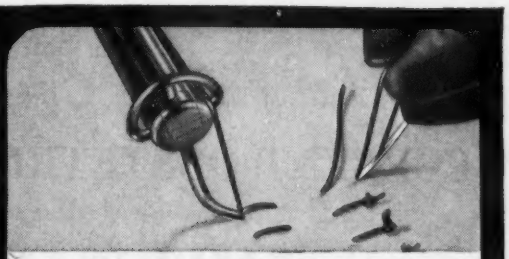

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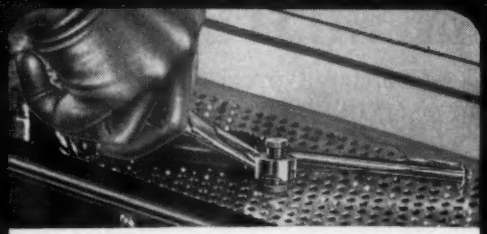

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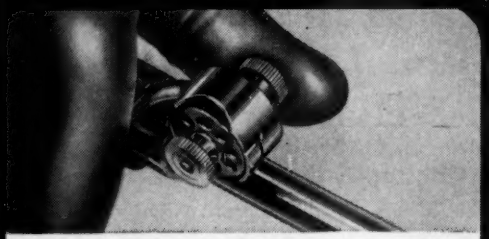

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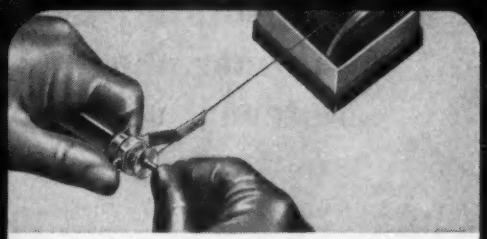

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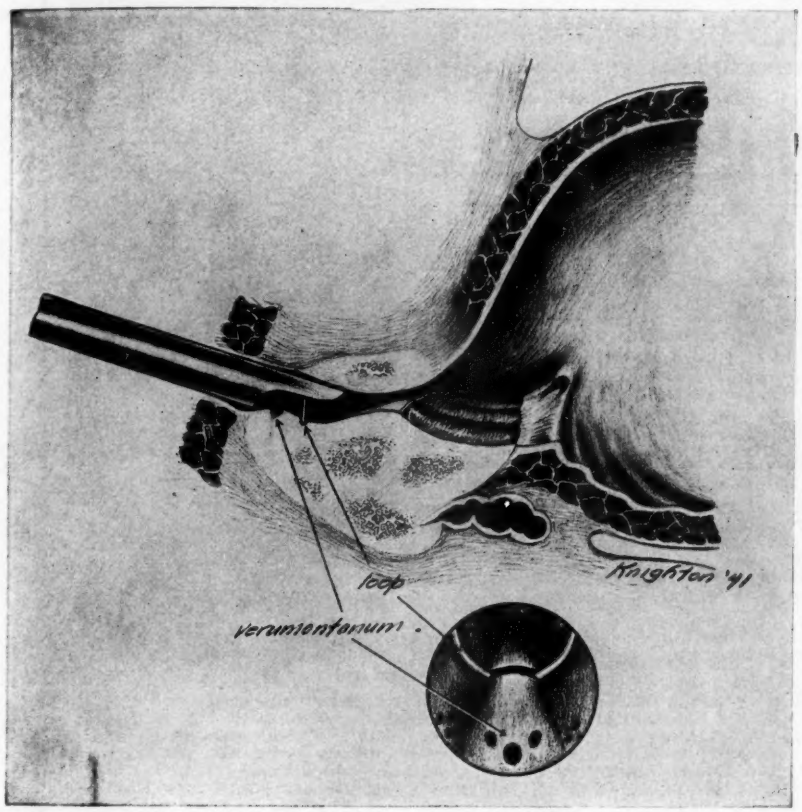

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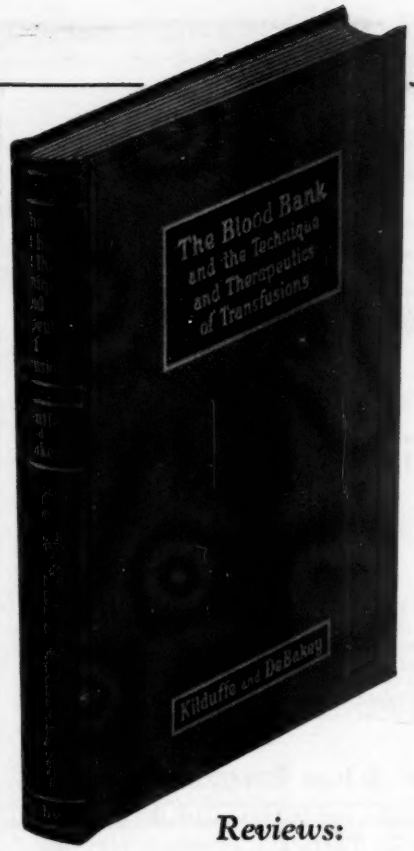

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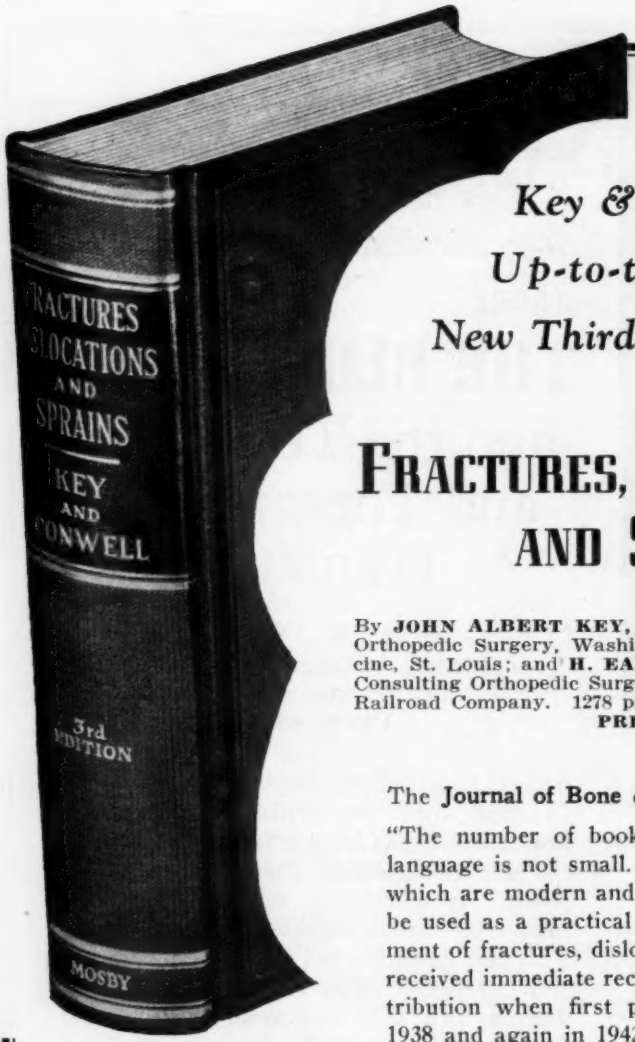

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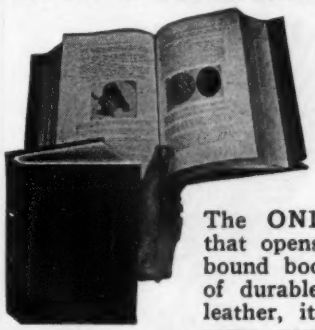

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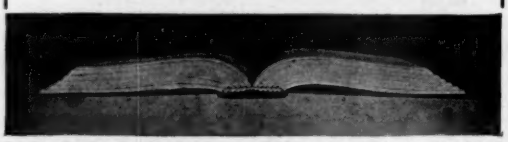

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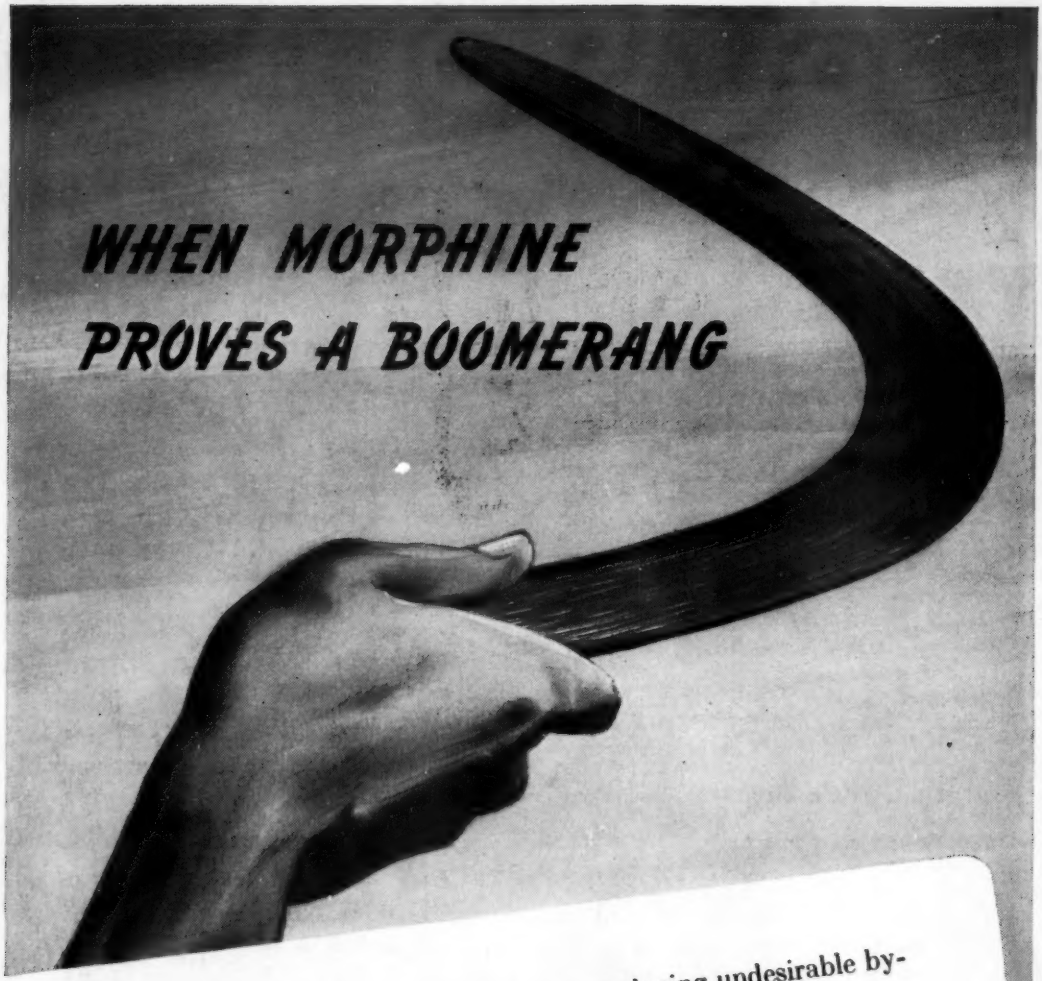

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